A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Multiple-Center Study with Additional Open-Label Single-Blind and Placebo-Controlled 24-Week Histology Cohorts to Evaluate the Safety, Tolerability, and Efficacy of NGM282 Administered for Up to 24 Weeks in Patients with Histologically Confirmed Nonalcoholic Steatohepatitis (NASH)

Protocol Number 15-0105 NCT02443116

for

NGM Biopharmaceuticals Australia Pty Ltd

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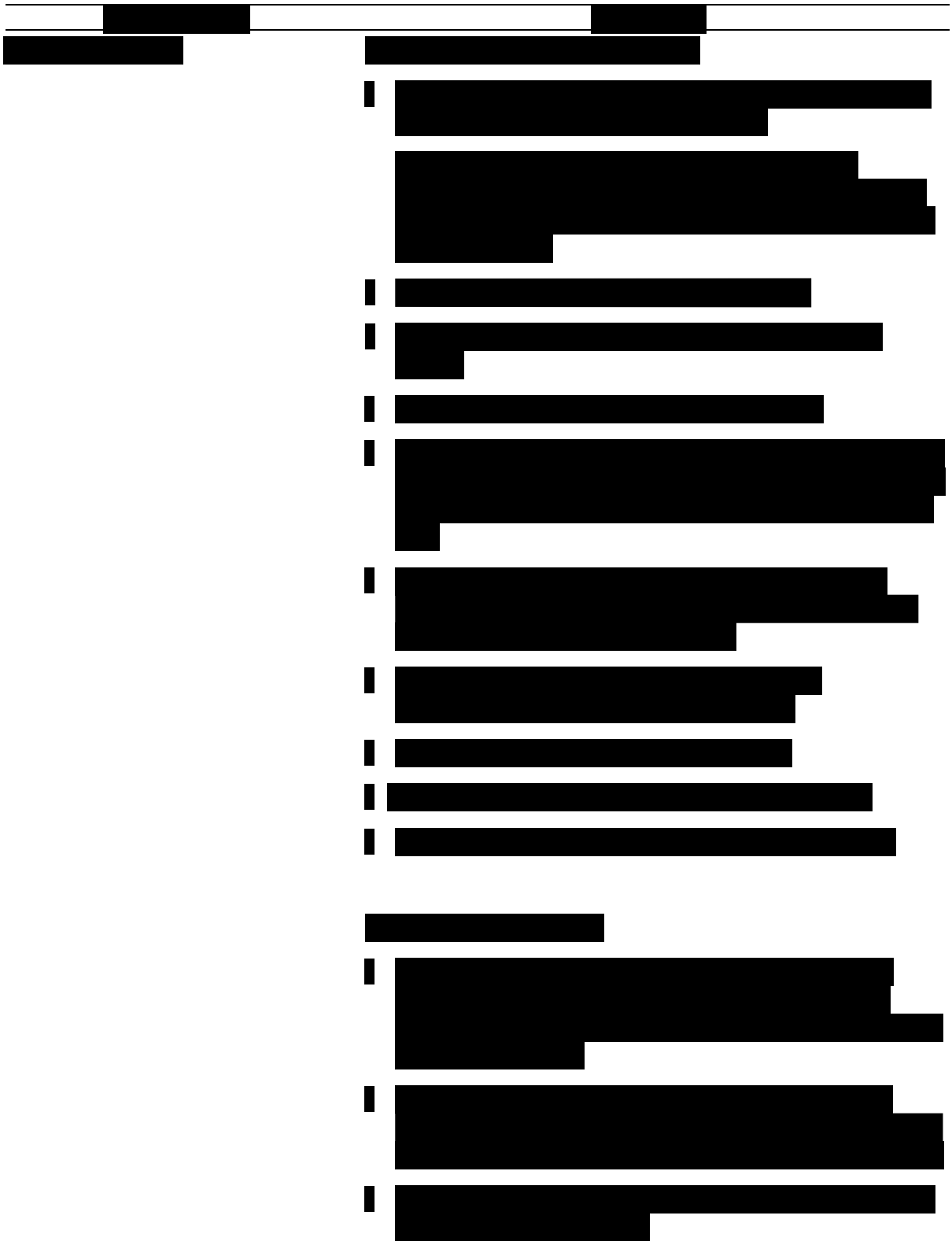
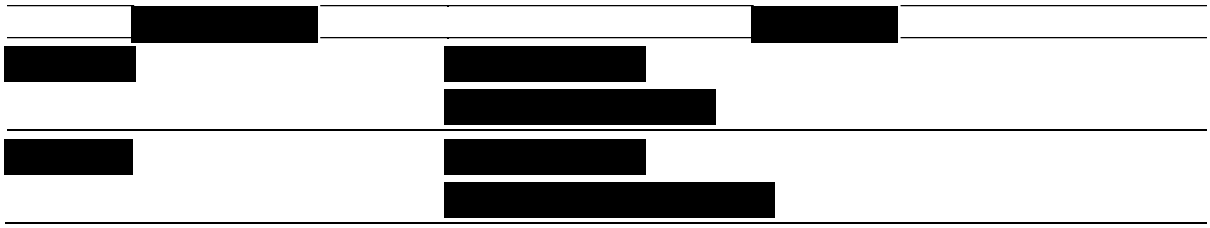
1 Study Identification

Sponsor:	NGM Biopharmaceuticals Australia Pty Ltd care of Grant Thornton Australia Ltd The Rialto, Level 30 525 Collins St. Melbourne, VIC 3000 +1 (650) 243-5555 (U.S. Telephone No.) +1 (888) 920-7929 (U.S. Facsimile No.) +61 (03) 9223 1118 (AUS Telephone No.) +61 (02) 9475 0798 (AUS Facsimile No.)
Sponsor's Study Manager:	[redacted] Clinical Project Manager NGM Biopharmaceuticals, Inc. 333 Oyster Point Blvd. South San Francisco, CA 94080 [redacted]
Sponsor's Medical Monitor:	[redacted] Sr. Director, Clinical Development NGM Biopharmaceuticals, Inc. 333 Oyster Point Blvd. South San Francisco, CA 94080 [redacted]

2 [redacted]





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3.3 List of Abbreviations

Abbreviation	Definition/Term
AAV	Adeno-associated virus
ADA	Anti-drug antibody
AE	Adverse event
AFP	Alpha fetoprotein
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration–time curve
AUS	Australia
BMI	Body mass index
$C_{2h\ post\text{-}dose}$	Concentration at 2 hours post-dose
C4	7-alpha-hydroxy-4-cholesten-3-one
CBC	Complete blood count (hematology clinical laboratory evaluations)
CHMP	Committee for Medicinal Products for Human Use (European Medicines Agency)
CI	Confidence interval
CL/F	Clearance divided by the bioavailable fraction
C_{max}	Maximum drug concentration
CRA	Clinical Research Associate
CRF	Case Report Form
CRN	Clinical Research Network
C_{trough}	Trough concentration
CTCAE	Common Terminology Criteria for Adverse Events
DIO	Diet-induced obese
EC	Ethics Committee
ECG	Electrocardiogram
ELF	Enhanced liver fibrosis
EOS	End of study
EOT	End of treatment
ER	Emergency room
FDA	Food and Drug Administration
FFA	Free fatty acid
FGF19	Fibroblast growth factor 19
FXR	Farnesoid X receptor
GGT	Gamma-glutamyl transpeptidase
GI	Gastrointestinal
GLP	Good Laboratory Practice
GLP1	Glucagon-like peptide-1
GRE	Gradient recalled echo
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein-cholesterol
HIV	Human immunodeficiency virus
HOMA-IR	Homeostasis model assessment–estimated insulin resistance
hr	Hour(s)
[redacted]	[redacted]
IA	Interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IL-6	Interleukin 6
INR	International Normalized Ratio
ISR	Injection-site reaction

Abbreviation	Definition/Term
ITT	Intent-to-treat
IWRS	Interactive Web Response System
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein-cholesterol
LIF	Liver Inflammation Fibrosis
LISSA	Local injection-site symptom assessment
LLT	Lowest Level Term (MedDRA)
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MRE	Magnetic resonance elastography
MRI	Magnetic resonance imaging
MRI-PDFF	Magnetic resonance imaging–proton density fat fraction
NAb	Neutralizing antibody
NAFLD	Nonalcoholic fatty liver disease
NAS	NAFLD Activity Score
NASH	Nonalcoholic steatohepatitis
NGM	NGM Biopharmaceuticals, Inc.
NGM282	Recombinant protein of 190 amino acids; engineered variant of humanized FGF19
NIH	National Institutes of Health
No.	Number
NOAEL	No-observed-adverse-effect level
NPO	Nothing by mouth
NZW	New Zealand White
OCA	Obeticholic acid
PBC	Primary biliary cirrhosis
PD	Pharmacodynamics; pharmacodynamic
PDFF	Proton density fat fraction
PI	Principal Investigator
PK	Pharmacokinetics; pharmacokinetic
PT	Preferred term
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SOC	System organ class
SOP	Standard Operating Procedure
$t_{1/2}$	Apparent terminal elimination half-life
T2D	Type 2 diabetes
TEAE	Treatment-emergent adverse event
TG	Triglyceride
TGF-β	Transforming growth factor beta
T_{max}	Time to maximum concentration
UA	Urinalysis
ULN	Upper limit of normal
U.S.	United States
V_z/F	Volume of distribution based on the terminal portion of the concentration–time curve divided by the bioavailable fraction
Wk	Week

4 Synopsis

Title of Study:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Multiple-Center Study with Additional Open-Label Single-Blind and Placebo-Controlled 24-Week Histology Cohorts to Evaluate the Safety, Tolerability, and Efficacy of NGM282 Administered for Up to 24 Weeks in Patients with Histologically Confirmed Nonalcoholic Steatohepatitis (NASH)
Protocol Number:	15-0105
Phase:	2
Investigational Product:	NGM282
Objectives:	Primary Objective: • Evaluate the treatment effect of NGM282 on absolute liver fat content as measured by magnetic resonance imaging–proton density fat fraction (MRI-PDFF) in patients with histologically confirmed NASH. Secondary Objectives: • Assess the safety and tolerability of NGM282 in patients with NASH with up to 24 weeks of treatment with NGM282. • Evaluate the percentage change in absolute liver fat content at End of Treatment (EOT). o In the open-label single-blind cohort, additional evaluations will be performed at Weeks 6 and 18 weeks o In the placebo-controlled 24-week histology cohort, additional evaluations will be performed at Weeks 6, 24, and 30 weeks • Evaluate the percentage of normalization for liver fat content at EOT. • Evaluate the change in liver fat content response rate as defined by a ≥ 5% decrease in absolute liver fat content. • Evaluate the absolute and percentage changes from Baseline to EOT as well as the percentage of normalization of the following parameters: ALT, AST, triglycerides, bilirubin (total and direct), and GGT. Percentage of normalization will also be investigated for a clinically meaningful threshold for triglycerides. • Evaluate the absolute and percentage changes from Baseline to EOT of the following (if collected as part of the cohort): o Total cholesterol, HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), triglycerides, and lipoprotein particles ▪ In addition, evaluate the absolute and percentage change from Baseline to End of Study (EOS) of the above lipid parameters in the open-label single-blind cohort. o [redacted] o Fasting blood glucose, insulin levels, [redacted], and homeostasis model assessment–estimated insulin resistance (HOMA-IR) o PRO-C3 and ELF Score (Placebo Controlled 24 Week Histology Cohorts) o Body weight, body mass index (BMI), and waist circumference o 7-alpha-hydroxy-4-cholesten-3-one (C4) and serum bile acids

	○ Bile-mediated absorption as measured by vitamin D, International Normalized Ratio (INR), and fecal fat content
Objectives (cont'd):	• Evaluate liver histologic response in Placebo Controlled 24 Week Histology Cohorts ○ Improvement in liver fibrosis by ≥ 1 stage by NASH Clinical Research Network (CRN) criteria with no worsening of steatohepatitis ○ Resolution of NASH (defined as an NAS score of 0 or 1 for inflammation and 0 for ballooning) with no worsening of fibrosis as determined by the NASH CRN criteria. • Evaluate the exposure of NGM282 in patients with NASH. ○ In the double-blind and placebo-controlled 24-week histology cohorts, NGM282 exposure will be compared to placebo at 2 hours post-dose at Day 1 and EOT and pre-dose at all on treatment study visits. ○ In the open-label single-blind cohort, NGM282 exposure will be evaluated at 2 hours post-dose at Day 1 and EOT and pre-dose at all on-treatment study visits. Additional PK samples will be collected at Baseline and 1, 2, 4, 8, and 12 hours post-dose on Day 1 and Week 6 in a subset of subjects in each dosing group. ○ Exposure of all doses from all cohorts will be compared to each other as well as to exposure in other study populations treated with NGM282 (Studies 12-0101, 13-0102, 13-0103, 14-0104, and 15-0106). • Evaluate the efficacy and safety of rosuvastatin administered in response to increases in total cholesterol and LDL-C from NGM282 treatment (open-label single-blind and placebo-controlled 24-week histology cohorts only). • Compare the dose-related changes in the safety, tolerability, PK, and pharmacodynamic (PD) parameters within and across the double-blind and open-label single-blind cohorts. Exploratory Objectives: • [redacted]

Methodology/ Study Design:	This is a multiple-center evaluation of NGM282 in a randomized, double-blind, placebo-controlled, parallel-group cohort with additional open-label single-blind and placebo-controlled 24-week histology cohorts when administered for up to 24 weeks as an SC injection in patients with histologically confirmed NASH. **In the double-blind cohort,** ~75 patients will be randomized across ~20 sites worldwide. Patients to be studied will have histologically confirmed NASH as defined by the NIH NASH Clinical Research Network and determined by a qualified local pathologist. Historical biopsy results within 6 months of Screening may be used for inclusion into the study; otherwise, a liver biopsy must be obtained for assessment. Patients must have a nonalcoholic fatty liver disease (NAFLD) activity score (NAS) of at least 4, with 1 point in each of the three components, along with the presence of fibrosis. Patients with cirrhosis will be excluded from this study. Patients will undergo an MRI during the Screening period, which must demonstrate at least 8% total fat content.

Methodology/ Study Design (cont'd):	On Day 1, subjects will be randomized into one of the three treatment arms (NGM282 3 mg, NGM282 6 mg, or placebo) in a 1:1:1 ratio. Subjects will be stratified at randomization according to non-diabetic and diabetic status at Day 1 to ensure an even distribution across the three groups. Study-drug self-administration instructions and training will be provided to the subjects and a weekly study-drug kit will be dispensed. Treatment assignment will be blinded to the sites, study subjects, sponsor, and Medical Monitor throughout the study period. The first dose (Day 1) and doses at Weeks 1, 2, 4, 8, and 12 will be self-administered in the clinic, with all other doses through Week 12 self-administered at home. Self-administration should occur in the morning for every dose in both the clinic and at home. Subjects will return to the clinic on Weeks 1, 2, 4, and 8 for on-treatment assessments and to receive weekly NGM282 study-drug kits. Week 12 will be the EOT clinic visit. Subjects will return to the clinic at Week 16 (or 4 weeks after last dose) for an EOS follow-up visit. Subjects are requested to undergo MRI performed during Screening and at Week 12 (EOT)/Early Withdrawal visit. **In the open-label single-blind cohort**, up to 100 patients (25 per dosing group) will be enrolled from ~6–8 U.S. sites. Subjects will be required to meet enrollment criteria similar to those of the double-blind cohort with the exception of the following, specifically defined in protocol Section 8.1.2: 1) historical biopsy window extended to 12 months; 2) limitations on the use of glucagon-like peptide-1 (GLP1) agonists; 3) glycated hemoglobin (HbA1c) level ≤ 9.5%; 4) LDL levels at Screening need to be ≤ 165 mg/dL; 5) exclusion of specific lipid-lowering therapies prior to and during study period; 6) no contraindications to receiving statins. The single-blind cohort is not randomized. At Day 1 eligible patients will be sequentially enrolled into the study and categorized as either statin-naïve versus statin experienced with no more than 8 statin experienced subjects within each dosing group. Subjects will be enrolled sequentially initially into the dosing Group 1 and enrollment will be continuous within the dosing group. Sequencing of the subsequent 2 dosing groups will be based on PD and safety parameters from dosing Group 1. The subsequent 2 dosing groups may run in parallel. A fourth optional dosing group may be conducted based on the safety/tolerability, imaging data, and histology (dosing Group 3 only) data from the prior 3 dosing groups. Dosing Group 4 will be initiated only after all subjects in Dosing Group 3 have been enrolled and a minimum of 10 subjects have completed 12 weeks of treatment in order to do a preliminary review of key data. Individual subject treatment assignment will be blinded only to the study subjects throughout the study period. The first dose of NGM282 (Day 1) and doses at Weeks 2, 4, 6, 8, and 12 study visits will be self-administered in the clinic, with all other doses throughout the treatment period self-administered at home. Self-administration of NGM282 should occur in the morning for every dose in both the clinic and at home. Subjects will return to the clinic on Weeks 2, 4, 6, and 8 for on-treatment assessments and to receive weekly NGM282 study-drug kits. LDL-C will be evaluated at Weeks 2, 4, and 8 in all subjects for possible increases in lipid levels associated with NGM282 administration. Rosuvastatin will be started in subjects meeting specific LDL-C level criteria. The specific dosing and administration of rosuvastatin will be based on whether the subject is statin naïve versus statin experienced and LDL-C levels at Weeks 2, 4, and 8. The dosing algorithms are specifically outlined in Section 10.4 of the study protocol. Bottles of rosuvastatin tablets will be dispensed at Weeks 2, 4, and 8, depending on observed lipid levels and dosing algorithm in Section 10.4. Week 12 will be the EOT clinic visit and subjects will return to the clinic at Week 18 (or 6 weeks after last dose) for an EOS follow-up visit. Subjects are required to undergo MRI performed during Screening and at Weeks 6, 12 (EOT)/Early Withdrawal, and 18 (EOS) visits. Dosing Groups 3 or 4 will have two other assessments performed to assess liver histology in addition to MRI-PDFF. LiverMultiScan™ will be performed during the MRI assessments at the same time as the MRI-PDFF assessments (Screening and

Weeks 6, 12, and 18). An additional post-treatment liver biopsy will be performed at Week 12 (EOT). The purpose of this biopsy is to assess early changes in liver histopathology (including changes in the NAS, resolution of NASH, and changes in fibrosis) and compare and correlate to the liver imaging studies and key serum biomarkers collected during the study. The historical liver biopsy window for this subset of subjects will be 3 months prior to Screening. Patients who wish to participate in the study but do not agree to the second biopsy will be allowed to Screen and enroll for other dosing groups if still open and they meet enrollment criteria.

In the placebo-controlled 24-week histology cohort, up to 75 patients (50 active at a single dose of NGM282; 25 placebo) will be enrolled from ~8–10 U.S. sites and treated for 24 weeks with a 6-week safety follow-up. Subjects will be required to meet enrollment criteria similar to those of the open-label single-blind cohort as specifically defined in protocol Section 8.1.1 with the exception of the following: 1) only patients with Stages 2 and 3 fibrosis at Screening will be enrolled. At Day 1 eligible patients will be randomized into the study and stratified as either fibrosis stage 2 or 3. The dose of NGM282 to be studied will be 1 mg based on a comparative evaluation of the safety, non-invasive efficacy parameters, and histology from the completed 3 mg 12-week histology cohort (Dosing Group 3) with a sufficient subset of subjects from the ongoing 1 mg 12-week histology (Dosing Group 4) in the open-label single-blind cohort. The active dose selection for this cohort will be blinded to the study site and patients throughout the study.

The first dose of NGM282 or placebo (Day 1) and doses at Weeks 2, 4, 6, 8, 12, 18, and 24 study visits will be self-administered in the clinic, with all other doses throughout the treatment period self-administered at home. Self-administration of NGM282 should occur as close as possible to the same time each day for every dose. Subjects will return to the clinic on Weeks 2, 4, 6, 8, 12, and 18 for on-treatment assessments and to receive NGM282 or placebo study-drug kits. LDL-C will be evaluated at Weeks 2, 4, 8, and 12 in all subjects for possible increases in lipid levels associated with NGM282 administration. Rosuvastatin will be started in subjects meeting specific LDL-C level criteria. The specific dosing and administration of rosuvastatin will be based on whether the subject is statin naïve or statin experienced and LDL-C levels at Weeks 2, 4, and 8 ((LDL-direct may be used if LDL-C was not able to be analyzed). A decision about possible second-line lipid-lowering therapy with ezetimibe will be made on a case by case basis for subjects that have not achieved an adequate response or are unable to tolerate rosuvastatin. The dosing algorithms are specifically outlined in Section 10.4 of the study protocol. Bottles of rosuvastatin tablets will be dispensed at all study visits depending on observed lipid levels and dosing algorithm in Section 10.4. Week 24 will be the EOT clinic visit and subjects will return to the clinic at Week 30 (or 6 weeks after last dose of NGM 282 or placebo) for an EOS follow-up visit. Subjects are required to undergo MRI performed during Screening and at Weeks 6, 12, 24 (EOT)/Early Withdrawal, and 30 (EOS) visits.

This cohort will have two other assessments performed to assess liver imaging histology in addition to MRI-PDFF. [redacted] n additional post-treatment liver biopsy will be performed at Week 24. The purpose of this biopsy is to assess changes in liver histopathology (including changes in the NAS, resolution of NASH, and changes in fibrosis) vs. baseline and to compare and correlate to the liver imaging studies and key serum biomarkers collected during the study.

Number of Patients:	Approximately 75 patients (25 per treatment group) will be randomized in the double-blind cohort. Up to 100 additional patients (25 per treatment group) will be enrolled in the open-label single-blind cohort. Approximately 75 additional subjects (50 active, 25 placebo) will be enrolled in the placebo-controlled 24-week cohort.
Number of Study Sites:	Double-blind cohort: ~20 sites worldwide Open-label single-blind cohort: ~6–8 U.S. sites Placebo-controlled 24-week histology cohort : ~10 U.S. sites
Test Product(s), Dose, and Mode of Administration:	For the double-blind cohort, the NGM282 final product will be supplied in pre-filled syringes intended to deliver 0.3 mL (3 mg) or 0.6 mL (6 mg) for SC injection. Placebo will be provided in volume-matched syringes (0.3 mL and 0.6 mL). For the open-label cohort, NGM282 final product will be supplied in pre-filled syringes intended to deliver 0.3 mL (0.3 mg, 1 mg, and 3 mg) for SC injection. For the placebo-controlled 24-week histology cohort, NGM282 final product will be supplied in pre-filled syringes intended to deliver 0.3 mL (1 mg) dose for SC injection. All subjects will be instructed to dose NGM282 each morning and to skip the dose if it is past 12:00 noon and administer the next dose as planned the following morning. The open-label single-blind and placebo-controlled 24-week histology cohorts will also include treatment with rosuvastatin for subjects meeting pre-specified LDL-C criteria. Study-labeled rosuvastatin 20-mg tablets will be supplied in order to deliver either 20 mg or 40 mg total daily doses as outlined in Section 10.4 to manage possible LDL-C increase during NGM282 treatment. The placebo-controlled 24-week histology cohort only will also include treatment with ezetimibe co-therapy that will be prescribed by the Investigator when subjects have not achieved an adequate LDL-C response or when subjects are unable to tolerate rosuvastatin. Ezetimibe is formulated as 10 mg tablets and can be administered with or without food at the same time as rosuvastatin and NGM282 or placebo
Duration of Treatment:	In all cohorts, patients will sign the Informed Consent Form at the Screening Visit, and will undergo screening assessments to verify eligibility for the study for up to 4 weeks from consent date. In the double-blind cohort, all subjects will be treated with NGM282 or placebo for 12 weeks and will be monitored for 4 weeks after completing their final dose of NGM282 or placebo. In the open-label single-blind cohort, subjects will receive NGM282 in 0.3 mg, 1 mg, or 3 mg doses for 12 weeks and be monitored for 6 weeks after completing final study-drug dose. In the placebo-controlled 24-week histology cohort, subjects will receive NGM282 or matching placebo at 1mg dose for 24 weeks and be monitored for 6 weeks after completing final study-drug dose. The total duration of individual participation will be ~20 weeks for the double-blind cohort, ~22 weeks for the open-label single-blind cohort, and ~34 weeks for the placebo-controlled 24-week histology cohort.
Criteria for Evaluation: Safety	In all study cohorts, safety and tolerability will be assessed by monitoring adverse events (AEs) and concomitant medications, conducting local injection-site symptom assessments (LISSAs), measuring vital signs and electrocardiograms (ECGs), and collecting and analyzing clinical laboratory blood and urine samples.

Criteria for Evaluation: Pharmacokinetics	In the double-blind cohort, PK will be analyzed to determine the steady-state trough and 2-hour post-dose NGM282 levels in NASH subjects and to compare to the levels in normal volunteers and in subjects with type 2 diabetes (T2D), and to explore PK/PD correlations in terms of drug efficacy (change in hepatic fat content), toxicity, and other parameters of the disease. In the open-label single-blind cohort, the same PK parameters and comparisons will be performed as outlined for the double-blind cohort. In addition, approximately 8 subjects per dosing group will be given the option to participate in further PK sampling at pre-dose and at 1, 2, 4, 8, and 12 hours after dosing on Day 1 and Week 6 in order to further characterize the PK in this population. In the placebo-controlled 24-week histology cohort, the same PK parameters and comparisons will be performed as outlined for the double-blind cohort.

Criteria for Evaluation: Efficacy & Pharmacodynamics	The primary efficacy endpoint for this study will be the absolute change in liver fat content as measured by MRI-PDFF in subjects with histologically confirmed NASH after 12 or 24 weeks of treatment. The following secondary endpoints will be investigated: Secondary Efficacy/PD/PK • Evaluate the percentage change in absolute liver fat content at End of Treatment (EOT). o In the open-label single-blind cohort, additional evaluations will be performed at Weeks 6 and 18. o In the placebo-controlled 24-week histology cohort, additional evaluations will be performed at Weeks 6, 24, and 30. • The percentage of responders (based on a liver fat content decrease ≥ 5%) at on-treatment and EOT • The absolute and percentage changes from Baseline by EOT of AST, ALT, bilirubin (total, direct), triglycerides, and GGT. Percentage of normalization by EOT will be investigated for ALT and triglycerides (including clinically meaningful normalization of triglycerides). • The absolute and percentage changes from Baseline at EOT of the following PD parameters: o [redacted] o Pro-C3 and ELF Score (Placebo Controlled 24 Week Histology Cohorts) o Fasting blood glucose, insulin levels, [redacted] and HOMA-IR o Body weight, BMI, and waist circumference o C4 and serum bile acids o Bile-mediated absorption as measured by vitamin D, INR, and fecal fat content • Percentage of liver histologic responders in Placebo Controlled 24 Week Histology Cohorts o Improvement in liver fibrosis by ≥ 1 stage by NASH Clinical Research Network (CRN) criteria with no worsening of steatohepatitis o Resolution of NASH (defined as an NAS score of 0 or 1 for inflammation and 0 for ballooning) with no worsening of fibrosis as determined by the NASH CRN criteria. • Evaluate the impact of rosuvastatin administered in response to increases in total cholesterol and LDL-C from NGM282 treatment. • Evaluate the dose-related changes in the safety, tolerability, PK, and PD parameters after up to 24 weeks of treatment. Pharmacokinetics • The exposure of 0.3, 1, 3, and 6 mg doses of NGM282 in subjects with NASH after up to 24 weeks of treatment Exploratory Endpoints • [redacted]

- [redacted]

Safety and Tolerability

- Safety and tolerability of NGM282 in subjects with NASH with up to 24 weeks of treatment through the prevalence of AEs, LISSA results, changes in clinical safety laboratory parameters, changes in vital signs, changes in ECGs, changes in physical examination, and the prevalence of concomitant medications
- Safety and tolerability of rosuvastatin in patients with NASH
- The absolute and percentage changes from Baseline at EOT of total cholesterol, HDL-C, LDL-C, and lipoprotein particles
- Ratios of key lipids and/or lipoprotein particles

Sample Size Determination:

A sample size of 75 patients was selected (25 patients per treatment arm) for the double-blind cohort design.

Allowing for a dropout rate of 10%, the following sample-size sensitivity calculations were based on a minimum number of 22 patients per treatment group completing the trial.

A 5% difference in total liver fat content is the minimal appreciable difference that would be considered clinically relevant between the active treatment arms and the placebo treatment group. If it is assumed that the NGM282 3-mg and 6-mg groups would have at least a 6% reduction in liver fat when compared to Baseline along with a reduction ≤ 1% from Baseline in the placebo group, with a 5% level of significance, the following illustrates sample-size power calculations based on varying common standard deviations to achieve an overall (overall F-test) statistically significant treatment effect:

	Mean Absolute Change from Baseline					
Method	NGM282 6 mg	NGM282 3 mg	Placebo	Common SD	Effect Size	Power
One-way analysis of variance (equal n's)	6%	6%	1%	8%	0.0868	54%
	6%	6%	1%	7%	0.1134	66%
	6%	6%	1%	6%	0.1543	80%
	6%	6%	1%	5%	0.2222	92%

SD = standard deviation.

A maximum sample size of 100 patients was selected (with a minimum of 15 patients per treatment arm, up to a maximum of 25 patients per treatment arm) for the open-label single-blind cohort design.

The sample size for the single-blind cohort was not based on a formal sample-size calculation. Instead, it was based on the results of the interim analysis that was conducted when ~15 patients per arm had completed 12 weeks of treatment. Although the results of this interim analysis are still blinded and the magnitude of the treatment differences observed indicate that a sample size of 15–20 patients per treatment arm is sufficient in order to give an initial indication of efficacy for further exploration.

Sample Size Determination (cont'd):	The sample size of the placebo-controlled 24-week histology cohort is based on 1) 12-week histologic response data from the 3-mg cohort and 2) estimated placebo histologic response rates from controlled Phase 2 studies in NASH. Preliminary 12-week histologic response data (n=16) demonstrated that 50% of subjects had a 1-stage improvement in fibrosis with no worsening of NASH or resolution of NASH with no worsening of fibrosis. The placebo histologic response rates from recent Phase 2b trials of obeticholic acid, cenicriviroc, liraglutide, and selonsertib were 14%–20% at timepoints ranging from 24 to 72 weeks. Based on these data, the assumptions of calculated sample-size estimates for 24-week efficacy used an NGM282 response of 50% versus 15% for placebo utilizing 80% power and alpha=0.05 with a 2:1 randomization scheme. Assuming a 15% drop-out rate, the planned sample size of 50 NGM282-treated subjects and 25 placebo subjects is sufficient to evaluate efficacy and support powering estimates for late-stage clinical trials.
Statistical Methods:	All patients who receive any amount of study drug will be included in the analyses, including those who withdraw prematurely from the study. Patients will be summarized within five analysis populations: • Intent-to-treat (ITT) population: all randomized patients (for the double-blind and placebo-controlled 24-week histology cohorts) • All Patients population: all enrolled patients (single-blind cohort only) • Safety population: all randomized/enrolled patients who receive at least one dose (full or partial) and have at least one post-dose safety evaluation • Efficacy population: all randomized/enrolled patients who receive at least one dose (full or partial) of study drug and have at least one valid, non-missing post-dose efficacy/PD parameter value • Per Protocol (PP) population: subset of patients in the Efficacy population; will include patients who have at least one valid, non-missing post-dose liver fat content measurement and excludes those patients who deviate from the conduct of the study or have an AE deemed by the medical monitor to be impactful on the primary endpoint • Liver histology population: subset of patients in the Efficacy population; will include patients who have at least one valid, non-missing Baseline and EOT biopsy and excludes those patients who deviate from the conduct of the study or have an AE deemed by the medical monitor to be impactful on the primary endpoint • PK population: all randomized/enrolled patients who receive at least one dose (full or partial) of drug, with a pre-dose (Baseline) blood draw, and at least one qualified (above the limit of quantification) post-dose sample The patient disposition will be presented by randomized treatment group for the double-blind and placebo-controlled 24-week histology cohorts and by enrolled treatment group for the single-blind cohort. The reasons for discontinuation will also be summarized. Treatment exposure will be summarized as extent of exposure to the study drug. Measures of extent of exposure will include the total number of doses per patient and compliance. Treatment exposure will be summarized using the Safety population by actual treatment group. Demographic and Baseline characteristics will be descriptively summarized by treatment group. Patient disposition, demographic, and Baseline characteristics will be summarized using the ITT population for the double-blind and placebo-controlled 24-week histology cohorts and using the All Patients population for the single-blind cohort.

Statistical Methods (cont'd):	The primary efficacy endpoint is the absolute change in liver fat content as measured by MRI-PDFF from Baseline to EOT. The absolute change from Baseline to EOT will be compared between treatment groups using an analysis of covariance (ANCOVA) model with treatment group and diabetic status (double-blind cohort only) as cofactors and Baseline absolute liver fat content as a covariate at the 5% level of significance. The primary endpoint will be evaluated using the Efficacy population and the analysis will be repeated using the Per Protocol population. The secondary and exploratory PD endpoints will be measured as an absolute as well as percentage change (for specific identified parameters) from Baseline to EOT. The secondary and exploratory PD endpoint analyses will utilize the Efficacy population. The absolute change and percentage change from Baseline to EOT will be compared between treatment groups using an ANCOVA model with treatment group and diabetic status (double-blind cohort only) as cofactors and Baseline endpoint value as a covariate at the 5% level of significance. In cases where the parameters do not follow a normal distribution, a non-parametric approach will be followed to analyze the difference between treatment groups. Categorical secondary endpoints (percentage of normalization) will be analyzed through a chi-square test. Further covariates/cofactors and correlations may be included in the modeling depending on the relevance to the endpoint analyzed and will be further described in the Statistical Analysis Plan. Safety and tolerability will be assessed by the following parameters: AEs, LISSAs, clinical laboratory tests, physical examinations, ECGs, vital signs, prior and concomitant medications. All safety analyses will be conducted using the Safety population. Apart from the lipid profile (total cholesterol, HDL-C, LDL-C, and lipoprotein particles), which will be analyzed as described for the primary and secondary endpoints above based on the safety population, all other safety endpoints will be analyzed descriptively only.
Interim Analyses:	A single interim analysis (IA) is planned to be conducted for the double-blind cohort after ~12 patients per arm have completed 12 weeks of treatment. The final analysis of the double-blind cohort will be conducted after all double-blind cohort patients have completed Week 16. The IA will include review of all safety and selected efficacy endpoints and is for internal planning purposes. The final analysis of the double-blind cohort will review all endpoints (safety, efficacy, and exploratory). The double blind will be maintained for the IA as the results in the summary tables will be presented only by treatment group. There will be no formal interim analysis of the open-label single-blind cohort. A single IA is planned to be conducted in the placebo-controlled 24-week cohort after at least 50% of the subjects (2:1 randomization) have completed 24 weeks of treatment. The IA will include review of safety and selected efficacy endpoints by treatment group. The IA is being conducted for internal planning purposes and the study will not be stopped early based on the results of the IA. Therefore, no formal hypothesis testing will occur with no effect on available alpha for the final planned analyses. The final analysis is planned to be conducted after all subjects have completed Week 30. Results for individual subjects will not be shared with study investigators. Further details of the IAs and final analyses, including statistical considerations and analyses, will be included in the SAP.

5 Introduction

5.1 Background

5.1.1 Nonalcoholic Steatohepatitis (NASH)

Nonalcoholic fatty liver disease (NAFLD) encompasses a spectrum of disease ranging from simple steatosis to inflammatory steatohepatitis (NASH). The estimated global prevalence of NASH has risen rapidly in parallel with the dramatic rise in population levels of obesity and diabetes, resulting in NAFLD now representing the most common cause of liver disease in the Western world (Swinburn 2011, Centers for Disease Control US Obesity Trends 2014). The prevalence of NASH is estimated to be between 2% and 5% in Western adults, rising to as high as 40%–50% in the morbidly obese patients with type 2 diabetes (T2D) (Argo 2009, Williams 2011). The histologic criteria for the diagnosis of adult NASH include macrovesicular steatosis, hepatocyte ballooning, and mild lobular inflammation (Kleiner 2005, Brunt 2009). Portal and periportal fibrosis followed by bridging fibrosis and cirrhosis are seen in patients with the progression of NASH. Steatosis may be absent in cases of bridging fibrosis or cirrhosis ("burnt-out NASH") and is often misdiagnosed as cryptogenic cirrhosis (Caldwell 2004). The NAFLD Activity Score (NAS) is a validated score used to grade disease activity in patients with NAFLD and NASH (Appendix A). The NAS is the sum of the biopsy's individual scores for steatosis (0–3), lobular inflammation (0-2), hepatocellular ballooning (0–2), and fibrosis (0–4). Fibrosis staging is assessed using a separate scoring system from the NAS (Kleiner 2005).

Most patients with NASH are asymptomatic, although some patients may present with fatigue, malaise, and vague right-upper abdominal discomfort. Patients are more likely to initially be identified by elevated liver aminotransferases on routine exams or hepatic steatosis detected incidentally on abdominal imaging. Patients with NASH often have one or more components of the metabolic syndrome such as obesity, hypertension, dyslipidemia, and insulin resistance or T2D, with NASH considered to be the hepatic manifestation of metabolic syndrome (Torres 2012). Most patients are diagnosed with NASH in their forties or fifties. Studies vary with regard to the sex distribution of NASH, with some studies suggesting it is more common in women while others suggest it is more common in men (Pan 2014). There appear to be ethnic differences in the prevalence of NASH, with a higher prevalence of hepatic steatosis in Hispanics compared with whites or blacks (Pan 2014).

The pathogenesis of NASH and progression to fibrosis/cirrhosis is not yet fully understood, despite recent advances in understanding complex metabolic and inflammatory pathways that are likely involved in disease progression. The most widely supported theory implicates insulin resistance as the key mechanism leading to hepatic steatosis and subsequent NASH (Cusi 2012). This is likely followed by oxidative injury resulting in the necroinflammatory component of NASH (Cusi 2012). Hepatic iron, antioxidant deficiency, and intestinal

bacteria have all been suggested as potential oxidative stressors (Cusi 2012). Several other factors known to be involved in the progression of NASH include inflammatory cytokines, adipokines, lipotoxicity, autophagy, and mitochondrial dysfunction (Tsochatzis 2009). There is also growing evidence of a genetic component for the progression of NAFLD to NASH as well as fibrogenesis in patients with NASH (Mehta 2014).

The natural history of NASH is variable from patient to patient and the NAS does not appear to be predictive of disease progression. The presence of fibrosis has been the only highly predictive factor of patients who will progress to cirrhosis. Approximately 10%–20% of patients with NAFLD will progress to NASH over a 7-year period (Argo 2009, Bhala 2013). Of these patients, roughly 20% will progress to cirrhosis over a 20-year period (Bhala 2013). A recent meta-analysis of paired biopsy studies in NASH patients demonstrated an annual fibrosis progression rate of 0.14 fibrosis stages in patients with NASH and 1 stage of progression over 7.1 years for patients with NASH (Singh 2014). The mortality rate of patients with NASH has been estimated at 1%–2% per year in patients with fibrosis, largely due to cardiovascular disease followed by liver-related causes (Kim 2013). Patients with NASH-related cirrhosis can progress to decompensated liver disease, complications of portal hypertension, and hepatocellular carcinoma (HCC). Recently, a growing number of cases of HCC in NASH patients have been reported without bridging fibrosis or cirrhosis, suggesting an independent pathogenic mechanism in this population (Paradis 2009). NASH is rapidly growing as the primary cause of end-stage liver disease in the U.S. and European populations and is expected to be the primary indication for liver transplantation by 2020 (Charlton 2011, Afzali 2012).

5.1.2 Treatment of NASH

The identification of a single therapeutic target has been complicated by the complexity of the pathogenesis of NASH. The treatment goals for NASH have focused on the prevention or reversal of liver injury either by treating the underlying metabolic and inflammatory conditions or through directly targeting fibrogenic pathways. Early-stage disease treatments have focused on insulin sensitization, decreasing lipids, and antioxidant activity. The endpoints for these treatments have been both improvements in biochemical parameters and histologic improvement in the components of NAS with no worsening or improvement of fibrosis. More recently, the resolution of NASH on biopsy has been considered a more clinically meaningful treatment endpoint. Antifibrotic agents have targeted the advanced fibrosis and cirrhotic populations but have little activity on the underlying disease causing the chronic hepatic injury.

Weight loss through lifestyle management is considered the first-line treatment strategy for NASH and is associated with improvement in liver histology and a reduction in cardiovascular and metabolic complications (Promrat 2010; Glass 2015). However, the majority of patients are unsuccessful in achieving or maintaining adequate weight loss and

require other interventions. In cases of morbid obesity, bariatric surgery has been successful in reversing the metabolic and hepatic injury associated with NASH (Cazzo 2014). Currently, no agents have been approved by regulatory authorities for the treatment of NASH; the majority of interventions have utilized agents approved for other indications. However, the interpretation of the data with many of these agents has been complicated by the study designs and endpoints. The majority of studies are uncontrolled or retrospective cohorts, have small sample sizes and/or are insufficiently powered, were comprised of heterogeneous populations, have treatment durations too short (<12 months) to demonstrate a treatment effect, and lack consistent definitions of response. Evaluated agents including metformin, fibrates, ursodeoxycholic acid, and orlistat have failed to show a significant histologic benefit in NASH (Torres 2012). Pilot studies with PPAR-γ agonists (pioglitazone, rosiglitazone) have been undertaken based on their effects on insulin resistance, inflammatory signaling, and fibrogenesis. Both agents have demonstrated improvements in ALT and steatosis with pioglitazone having a marginally better anti-inflammatory and anti-fibrotic activity (Belfort 2006, Neuschwander-Tetri 2003). Vitamin E has also been evaluated in NASH patients based on its antioxidant properties. Small pilot studies have demonstrated histologic improvement with daily doses of 400–800 IU (Harrison 2003). The PIVENS trial comparing pioglitazone or vitamin E to placebo was the first well-controlled study to show an impact on steatosis, inflammation, hepatocyte ballooning, and fibrosis, with vitamin E having slightly better improvements in fibrosis (Sanyal 2010). Although a treatment benefit was demonstrated in this study, the improvements in fibrosis were modest. Additionally, near- and long-term safety and tolerability concerns were observed with both pioglitazone (weight gain, edema, bone fractures, malignancy) and vitamin E (hemorrhagic stroke, inhibition of platelet aggregation, malignancy). More recently, the farnesoid X receptor (FXR) agonist obeticholic acid (OCA) was evaluated in the FLINT trial in a population similar to that in the PIVENS study with comparable primary and secondary endpoints (Neuschwander-Tetri 2014). OCA demonstrated results comparable to vitamin E versus placebo in terms of improvements in NAS and fibrosis whereas vitamin E and pioglitazone demonstrated better results compared to OCA in terms of resolution of NASH. Additionally, significant increases in pruritus and lipids (requiring treatment on study) were associated with OCA. Although these agents have demonstrated some histologic improvement in NASH, a significant medical need for new effective therapies with favorable safety and tolerability profiles remains.

5.1.3 Therapeutic Rationale for NGM282 in NASH

The pathogenesis of NASH involves complex interactions of insulin resistance, dysregulation of lipid and triglyceride metabolism, and bile acid synthesis that leads to steatohepatitis and fibrogenic activity. The biologic activity of the fibroblast growth factor 19 (FGF19) can

potentially impact all of these mechanisms to a varying degree, supporting the evaluation of the therapeutic applications of this pathway for the treatment of NASH.

FGF19 is a naturally occurring protein selectively expressed and secreted in the gastrointestinal (GI) tract. Studies have shown that the predominant expression is in the ileum with some expression observed in the brain, retina, cartilage, and skin (Schauer 2003, Cummings 2007).

FGF19 acts as an endocrine hormone to regulate systemic glucose homeostasis and bile acid synthesis (Schauer 2003). FGF19 is released postprandially from the distal small intestine into the circulation and functions as a hormone to govern hepatic glycogen synthesis and gluconeogenesis without stimulation of lipogenesis (Kir 2011, Potthoff 2011). In normal human subjects, the basal level of systemic FGF19 concentration ranges between 200 and 400 pg/mL (Lundasen 2006, Stejskal 2008). Systemic FGF19 levels are decreased in patients with T2D or metabolic syndrome and are normalized after bariatric surgery in diabetic human subjects (Mingrone 2012).

In mouse models of diabetes and/or obesity, transgenic or viral-mediated FGF19 expression resulted in profound metabolic benefits (similar to gastric bypass surgery), including the rapid resolution of hyperglycemia and hyperinsulinemia (Xie 1999). Transgenic mice over-expressing FGF19 are resistant to diet-induced obesity and have decreased body fat mass and improved insulin sensitivity, glucose disposal, and plasma lipid profiles (Tomlinson 2002). Subcutaneous (SC) administration of recombinant FGF19 protein into leptin-deficient mutant obese or diet-induced obese (DIO) mice results in similar metabolic effects (Fu 2004). Similar to insulin, FGF19 stimulates hepatic protein and glycogen synthesis but does not induce lipogenesis (Schauer 2012).

FGF19 has also been found to be associated with disease progression in NASH. Adult patients with biopsy-proven NAFLD and NASH have decreased serum levels of FGF19 (Eren 2012, Bechmann 2013). Additionally, decreased FGF19 serum levels are inversely correlated with severity of fibrosis/cirrhosis NASH-related liver disease (Alisi 2013). Although normal intestinal secretion of FGF19 occurs in NASH, hepatic β-klotho expression is reduced and hepatic response to FGF19 is impaired, and a correlation exists between increased hepatocyte ballooning and increased FGF19 levels (Schreuder 2010, Wojcik 2012). The increased understanding of the role of bile acids in the pathogenesis of NASH further supports the therapeutic potential of FGF19. Nonclinical models demonstrate a significant role of dysregulation of bile acid synthesis in the pathogenesis of NASH (Tanaka 2012, Jia 2013). Increased bile acid synthesis as well as serum bile acid and 7-alpha-hydroxy-4-cholesten-3-one (C4) concentrations, a key marker of CYP7A1 activity, correlate with NASH disease severity and fibrotic activity (Bechmann 2013). Altered bile acid composition has been observed in patients with NASH, with a compensatory transition from CYP7A1-mediated classic pathway (toxic bile acids) to the less toxic alternative

pathway (Lake 2013). Increased hepatic concentrations of bile acids are also associated with increased apoptosis, Fas, and TNF-R1 activity resulting in hepatocyte injury and stellate cell activation (Faubion 1999, Higuchi 2003). A significant correlation also exists between increases in specific bile acids and severity of NASH-related hepatic injury (Aranha 2008).

Based on the identified beneficial metabolic and bile acid synthetic activities of FGF19 in animal models, the associated reduction of FGF19 levels with obesity and diabetes in patients, the associated increase in plasma levels after gastric bypass in humans, and the clinical associations of FGF19 deficiency in NASH patients, the FGF19 biologic pathway represents a potentially important therapeutic target for the treatment of NASH.

NGM282 is a recombinant protein of 190 amino acids with a molecular weight of 21.3 kDa and an amino acid sequence 95.4% identical to that of human FGF19. Extensive in vivo structure–activity relationship analyses have been conducted to define and manipulate the distinct functional domains in FGF19 protein that are responsible for its metabolic and proliferative features. More than 160 variants of human FGF19 were engineered, of which NGM282 was selected as the clinical candidate based on robust efficacy with no evidence of the proliferative activity previously observed in *db/db* mice.

NGM282 effectively mimics the actions of FGF19 on glucose homeostasis as demonstrated in a series of in vitro and in vivo pharmacology studies. In vitro, NGM282 binds to the extracellular portion of mouse and human FGFR1c–β-klotho co-receptor complexes, with high nanomolar affinity (Study 11-MP-NGM282-1002). NGM282 has been shown to potently trigger FGFR1c-mediated intracellular signaling in mouse- and human-cultured adipocytes (Study 11-MP-NGM282-1001). NGM282 also activates intracellular signaling pathways in L6 cells transfected with FGFR1c–β-klotho complexes of the mouse, rat, rabbit, cynomolgus monkey (*Macaca fascicularis*), or human (Study 13-MP-NGM282-1004). In vivo, daily administration of NGM282 to *ob/ob* mice for 14 days resulted in significant dose-dependent reductions in the levels of non-fasting blood glucose (Study 11-PD-NGM282-1003). In DIO mice, fasted blood glucose levels were significantly reduced following a 14-day treatment regimen in response to NGM282 as low as the lowest dose tested (0.1 mg/kg) (Study 11-PD-NGM282-1004). NGM282 also effectively mimics the actions of FGF19 on bile acid synthesis through the binding of FGFR4c–β-klotho co-receptor (Study 12-MP-NGM282-1006). Bile acid homeostasis is regulated through gene expression of the CYP7A1 enzyme in hepatocytes by bile-acid–dependent synthesis of FGF15/19 in the intestine. In vitro studies have demonstrated that NGM282 binds to human hepatocytes with affinity similar to that of FGF19 (Studies 11-MP-NGM282-1002 and 13-MP-NGM282-1005). Additionally, NGM282 specifically inhibits only CY7A1 activity without inhibiting other bile-acid–synthetic enzymes (Study 12-MP-NGM282-1006). In vivo studies have shown that systemic administration NGM282 can potently and rapidly suppress the expression of the *Cyp7a1* gene in *db/db* mice (Study 11-PD-NGM282-1001). NGM282

has demonstrated a dose-dependent decrease of Cyp7a1 levels. Consistent with reduction in Cyp7a1 levels, serum C4 levels were also reduced in the 28-day monkey toxicology study (Study 11-TX-NGM282-1002) and 26-week toxicology study in monkeys (Study 13-TX-NGM282-1004). Significant reductions in serum C4 levels were also observed after administration of NGM282 in normal volunteers (Study 12-0101).

NGM282 has also been evaluated in two distinct animal models of NASH. Adeno-associated virus (AAV)–mediated delivery of NGM282 transgenes into FXR-deficient mice demonstrated improvement in the histologic, biochemical, and fibrogenic biomarkers associated with NASH-related hepatic injury (Study 13-PD-NGM282-1007). Similarly, AAV administration of NGM282 in the STAM™ model of NASH in mice showed a significant reduction in steatosis, inflammation, ballooning, and overall body weight versus placebo (data on file).

The safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of NGM282 have been studied in a blinded, placebo-controlled, single-ascending-dose (SAD)/multiple-ascending-dose (MAD) study in normal subjects (Study 12-0101). NGM282 or placebo was administered to 119 normal subjects as a daily SC injection in escalating doses of 0.1–30 mg in the SAD module and 0.1–20 mg in the MAD module. Multiple-dose PK were consistent with single-dose PK parameters, with no evidence of drug accumulation. NGM282 was safe and well tolerated with no serious adverse events (SAEs) or clinically relevant laboratory abnormalities. Mild to moderate injection-site reactions (ISRs) were the most common drug-related adverse events (AEs), observed mainly with higher doses and larger injection volumes. NGM282 had a favorable safety profile and highly predictable PK that support once-daily dosing.

NGM282 has recently been evaluated in 80 patients with T2D, many of whom have presumptive NASH (Study 13-0102). NGM282 was administered for 28 consecutive days in patients randomized into one of the four treatment conditions (NGM282 at doses of 2, 5, or 10 mg; or placebo). Dose-dependent improvement in insulin sensitivity and body weight, as well as decreases in triglycerides and ALT, were observed compared to placebo as well as a trend to a decrease in fasting blood glucose and a slight increase in HDL. Total cholesterol and low-density lipoprotein (LDL) were modestly increased with NGM282 at Day 28. This increase appears to represent an acute change at Day 14, followed by a decrease from Day 14 to Day 28, consistent with a mitigation of this rise over time. C4 was suppressed by > 95% in subjects treated with the 2- and 5-mg doses. NGM282 was well tolerated with no SAEs or safety signals observed during the study. Mild to moderate GI symptoms (nausea, loose stools) as well as mild ISRs were the most frequently reported AEs, both of which were seen more frequently at the higher doses. In general, NGM282 was well tolerated in a population with characteristics similar to those in patients with NASH.

Based on the identified activities in animal models as well as the PK and favorable safety and tolerability profiles in normal volunteers and T2D patients, NGM282 represents a potentially important therapeutic option for the treatment of NASH through enhanced FGF19 signaling.

5.2 Nonclinical Studies

NGM has completed a series of in vitro and in vivo nonclinical studies supportive of the clinical development of NGM282 in patients with NASH. Please refer to the Investigator's Brochure (IB) for additional information on these studies.

5.2.1 Nonclinical Safety Assessment

The nonclinical safety of NGM282 has been assessed in general toxicity studies in CD-1 mice and cynomolgus monkeys for up to 26 weeks of treatment and in embryo–fetal toxicity studies in CD-1 mice and New Zealand White (NZW) rabbits. NGM282 was pharmacologically active in the mouse and monkey for up to 26 weeks of treatment.

In the monkey, NGM282 was clinically well tolerated as clinical signs were limited to increased hair loss at doses ≥ 0.1 mg/kg and slight reductions in body-weight gain at 1 mg/kg at 26 weeks of treatment. In the mouse, NGM282 produced transient clinical signs (e.g., hypoactivity or partial eye closure) at doses ≥ 1 mg/kg that were not dose limiting and resolved with continued treatment for up to 26 weeks. In the mouse, microscopic findings were limited to the liver (minimal to moderate hepatocellular hypertrophy) that was associated with slight increases in albumin, total protein, and liver weight. These changes were not considered adverse and were reversible.

In the mouse and rabbit, NGM282 did not produce any adverse effects on embryo–fetal development at the highest doses tested (10 mg/kg). In the rabbit, the no-observed-adverse-effect level (NOAEL) was 1 mg/kg due to maternal toxicity associated with body-weight gain reduction and associated reduction in fetal uterine weight at 10 mg/kg.

Based on the cumulative nonclinical safety profile of NGM282 for up to 26 weeks of treatment, the NOAELs in the mouse and monkey were determined to be 1 and 3 mg/kg, respectively. A sufficient safety margin exists for NGM282 at the proposed maximal clinical dose of 6 mg (0.0864 mg/kg) where estimated exposure is estimated to be 2- or 14-fold below that at the NOAELs in the mouse or monkey, respectively (see Table 1).

Table 1. Estimated Safety Exposure Margin of NGM282

Nonclinical Species	NOAEL (mg/kg) [a]	Plasma AUC (hr • ng/mL) [b]	Exposure Margin Relative to Maximum Human Therapeutic Dose [c]
Monkey	1	6610	~14X
Mouse	3	1062	~2X

AUC = area under the concentration–time curve; hr = hour; NOAEL = no-observed-adverse-effect level.
[a] Determined from the 6-month chronic toxicity studies.
[b] Systemic exposure at Day 1 after a single dose was used as the most conservative estimate of exposure given the presence of anti-drug antibody formation with repeat dosing in animals leading to drug accumulation (plasma AUC 7-fold above Day 1 levels).
[c] Based on a maximal therapeutic dose of 6 mg (0.0864 mg/kg based on a 70-kg patient) where plasma AUC is projected to be 482 hr • ng/mL (Study 12-0101).

5.3 Clinical Studies

To date, NGM has completed a Phase 1 clinical study in healthy volunteers and Phase 2 clinical studies in T2D and primary biliary cirrhosis (PBC) supportive of the clinical development of NGM282 in patients with NASH. Additionally, blinded safety data from the ongoing Phase 2 clinical trial in NASH patients are also available to further support the open-label single-blind cohort. Please refer to the IB for additional detailed information on these studies.

5.4 Rationale for Dose Selection of NGM282 for NASH

The doses selected for the Phase 2 study are supported by both the nonclinical and clinical data generated to date. The dose range for the first-in-human Phase 1 clinical trial (0.1–30 mg) was based on a broad approach to dose calculation considering the pharmacology of FGF19, beyond sole reliance on the NOAEL obtained in the GLP 28-day toxicology program. The dose range also took into consideration safe starting-dose principles for first-in-human administration as outlined in both FDA and CHMP Guidance. Dose-proportional changes in PK parameters were observed with both single and multiple dosing in the Phase 1 study, consistent with predictions from animal models. All doses were safe and well tolerated, thus establishing the initial clinical safety of this dose range.

The proposed doses of 0.3, 1, 3, and 6 mg for evaluation in the double-blind as well as the single-blind cohorts are based on a cumulative broad approach to dose calculation considering the pharmacology of FGF19 in NASH, clinical data from normal volunteers and patients with T2D, and exposure safety margins obtained in the GLP 26-week toxicology program relative to the clinical doses proposed. The proposed doses for both cohorts are within the current safety margins in both monkeys and mice (Table 1). The drug exposure is comparable between normal volunteers and T2D patients and, therefore, expected to be comparable in the NASH population.

The selection of the 0.3, 1, 3, and 6 mg doses is further supported by the efficacy, safety, and tolerability observed in the T2D study in which NGM282 doses of 2, 5, or 10 mg were evaluated. The T2D study patients represent a population similar to the NASH population expected to be enrolled in the NASH Phase 2 study. In patients with T2D, doses > 2 mg are associated with greater decreases in body weight, fasting blood glucose, triglycerides, HDL, and ALT, all of which are parameters associated with potential therapeutic activity in NASH. The subsequent decreases in LDL at Day 28 after initial increases at Day 14 are greater with doses > 2 mg. A trend toward increased frequency and severity of GI symptoms and ISRs in patients treated with 10 mg was noted; therefore, lower doses were selected for tolerability. Lastly, bile acid synthesis as measured by suppression of C4 levels is greatest at doses of 3 mg based on the data from the Phase 1 normal volunteer study. Furthermore, C4 was suppressed by > 95% in T2D patients treated with the 2- and 5-mg doses of NGM282. Based on the above data, the selected doses should allow a balance of optimizing biologic activity versus safety and tolerability in the studied population.

The selection of the lower doses (0.3 mg and 1 mg) for study in the open-label single-blind cohort was based on the robust results of the double-blind cohort demonstrating comparable improvements in the non-invasive markers of NASH at 3 mg and 6 mg, with improved tolerability with the 3 mg dose. Subjects enrolled in the open-label single-blind cohort received 0.3 mg or 1 mg for 12 weeks in order to establish a minimally effective dose, based on non-invasive measures of liver fat, inflammation, and fibrosis. Additionally, based on the rapidity of the treatment effect demonstrated with 3 mg and 6 mg, [redacted] This demonstrated significant improvement in both NAS and fibrosis scores with 3 mg for 12 weeks. In order to assess the histologic response and utility of 1 mg, a 12-week biopsy dosing group (Group 4) is ongoing.

The selection of the 1 mg dose for the placebo-controlled 24-week histology cohort is based on a comparative evaluation of the histologic response, non-invasive parameters, and safety in the previous cohorts in Study 15-0105. Preliminary data from the first 10 subjects at 12 weeks from the 1 mg histology dosing group (Group 4) demonstrated comparable changes in non-invasive parameters (MRI-PDFF, LMS and ALT) and histology to the 3 mg histology dosing group (Group 3). Additionally, there were no new safety signals observed in either cohort. The 1 mg cohort had fewer injection site reactions as well as less persistent GI symptoms. Therefore, the 1 mg dose was selected to move forward into the placebo-controlled 24 week histology cohort based on the assessment of comparative risk benefit of the 1 mg and 3 mg doses.

5.5 Rationale for the Use of Rosuvastatin for Lipid Management in NGM282-treated Subjects

NGM282 specifically inhibits CYP7a similar to FGF19 through binding to FGFR4c–β-klotho complexes causing a potent and rapid suppression of cholesterol metabolism and a subsequent decrease in bile acid synthesis. The biologic activity of NGM282 is similar to FGF19 and has been shown to cause an increase in serum levels of total cholesterol and LDL-C to a varying degree in cynomolgus monkeys (data on file) as well as in normal volunteers (Study 12-0101) and T2D patients (Study 13-0102). More recent data from the blinded safety review in Study 15-0105 demonstrated similar elevations in NASH patients. The clinical outcomes associated with long-term elevations in LDL-C associated with NGM282 are unknown. However, the evaluation of lipid-lowering therapies, in particular statins, is warranted given the increased cardiovascular risk associated with the NASH patient population. The ability of statin therapy to mitigate FGF-19–mediated increases in LDL-C has been demonstrated in both primate and human studies. Recent data from obese insulin-resistant primates demonstrated that the increase in LDL-C levels seen with NGM282 was substantially reduced with rosuvastatin to pre-treatment baseline levels (data on file). OCA is an FXR agonist shown to cause increases in LDL-C in NASH patients (Neuschwander-Tetri 2014). The use of statins was demonstrated to be safe and well tolerated in this population receiving OCA; in addition, LDL-C levels decreased to near baseline. The co-administration of OCA and statins is currently being studied in a randomized, double-blinded clinical trial (NCT02633956). Therefore, the impact of statin co-therapy with NGM282-induced LDL-C elevations is warranted. Rosuvastatin was selected for its potency and demonstrated clinical effect on cardiovascular outcomes. Doses of 20 and 40 mg will be studied in order to evaluate any dose-dependent differences in activity in NGM282-treated subjects.

5.6 Rationale for MRI-PDFF, [redacted] Assessments

Improvements in steatosis have been demonstrated to be a key component of a therapeutic response and resolution of NASH. NGM is utilizing a change in total liver fat content of at least 5% as measured by magnetic resonance imaging–proton density fat fraction (MRI-PDFF) as a primary efficacy endpoint in the Phase 2 Study 15-0105 in NASH patients. MRI-PDFF has been determined to be more sensitive than histology for detecting changes in liver fat content in several natural history and therapeutic trials (Meisamy 2011). Additionally, it is non-invasive and provides quantitative estimates of fat content throughout the entire liver and is less operator dependent and more sensitive than either ultrasound or CT scan (Kang 2011, Permutt 2012). A reduction of at least 5% in absolute liver fat and 29% relative reduction in liver fat was associated with histologic improvements in NASH and is currently being utilized in several completed and ongoing clinical studies in NASH (Patel 2016). The double-blind cohort in Study 15-0105 is measuring change in liver fat by

MRI-PDFF at Baseline and Week 12 to assess the primary treatment effect. Data from T2D patients treated with NGM282 who had elevated liver enzymes demonstrated a rapid reduction in both liver enzymes and C4 after initiating treatment. Based on the rapid biologic activity observed, an additional on-treatment MRI has been added to the open-label single-blind cohort at Week 6 in order to assess the kinetics of fat loss at mid-treatment. An off-treatment MRI at Week 18 (EOS) has been added to this cohort as well in order to assess the reversibility of fat loss after stopping therapy. These effects will be further assessed over an extended duration in the placebo-controlled 24-week histology cohort with MRI-PDFF assessments collected at Screening and Weeks 6, 12, 24 (EOT), and 30 (EOS).

[redacted] The software uses the images of the liver to calculate parameters that have been shown to correlate with histological measures of steatosis, hepatic iron overload, and fibrosis of the liver (Banerjee 2014). Additionally, a Liver Inflammation Fibrosis (LIF) score and corrected cT1 valueare also calculated, both of which have been correlated to liver histology as well as predicting liver-related outcomes (Banerjee 2014, Pavlides 2016, Perspectum Diagnostics, data on file).

[redacted] There are no current imaging techniques that can directly detect the specific stage of fibrosis. Most attempt to detect fibrosis indirectly using proposed biomarkers which include: stiffness, diffusion, perfusion, metabolites, and image texture with the leading biomarker being liver stiffness (Younossi 2017). [redacted]

5.7 Rationale for a Liver Biopsy at Weeks 12 or 24

Liver biopsy remains the gold standard for assessing treatment effect in NASH patients, as measured by a resolution of steatohepatitis and/or an improvement in fibrosis. However, several non-invasive imaging technologies and biochemical markers have also correlated with improvements in liver histology. MRI-PDFF is a highly sensitive measure of steatosis with decreases in absolute and relative liver fat of 4.1% and 29.3%, respectively, correlating to > 2 point improvement in NAS after 24 weeks of ezetimibe (Patel 2016). On-treatment decline in ALT was associated with the resolution of NASH and no worsening of fibrosis in patients treated with elafibranor for 52 weeks (Ratziu 2016a). Similarly, a decrease in

triglycerides correlated with resolution of NASH after 96 weeks of pioglitazone or vitamin E (Corey 2015). Increased classic-pathway bile acid synthesis is associated with increased NASH severity and fibrosis (Bechmann 2013; Lake 2013). Decreases in bile acid synthesis, as measured by C4 levels, is observed with FGF19 activity seen with NGM282 and other investigational therapies (Marschall 2012, Djedjos 2016).

NGM282 was studied in 81 patients with type 2 diabetes (many with presumptive NASH) for 28 days at doses of 2, 5, or 10 mg versus placebo (Study 13-0102). Rapid and dose-dependent improvements in ALT, triglycerides, and C4 were observed compared to placebo, supportive of further evaluation in NASH. An analysis of the double-blind cohort of Study 15-0105 was performed on 43 subjects completing 12 weeks of treatment (Harrison 2017). Significant reductions in both absolute and relative liver fat were observed after only 12 weeks compared to placebo, with the majority of subjects normalizing liver fat content. ALT levels also declined rapidly, with significant reductions observed as soon as Week 2 and over 50% of subjects normalizing ALT by Week 12. Significant reductions of ALT, C4, and other key biochemical parameters associated with histologic response were also observed in NGM282-treated patients. In addition to the results of the non-invasive efficacy data, 12-week histology has also been evaluated in the 3-mg cohort using the FDA-accepted endpoints. Preliminary 12-week histologic response data demonstrated 50% of subjects had a 1-stage improvement in fibrosis with no worsening of NASH or resolution of NASH with no worsening of fibrosis. Histology assessments will be conducted at Week 12 in the open-label single-blind dosing Groups 3 and 4 and at Week 24 in the placebo-controlled 24-week histology cohort. The clinical data from these cohorts will provide information on the long-term safety and efficacy (histological and noninvasive) of NGM282 and support the late-stage development of NGM282 for treatment of NASH with fibrosis.

Although there are currently no approved therapies for the treatment of NASH, several late-stage compounds have demonstrated modest improvements in the resolution of NASH and/or fibrosis as well as decreases in key markers that correlate with these histologic changes. However, the treatment duration to achieve these changes is 24–72 weeks (Sanyal 2010, Neuschwander-Tetri 2014, Patel 2016, Ratziu 2016b, Sanyal 2016, Loomba 2016). The changes in MRI-PDFF, ALT, triglycerides, and C4 are significantly more rapid and of a greater magnitude by Week 12 versus other therapies for longer treatment periods. Therefore, early changes in histology may be observed supporting an early time-point for post-treatment liver histology assessment.

The primary objective of this additional histologic assessment in dosing Groups 3 or 4 of the open-label single-blind cohort and the placebo-controlled 24-week histology cohort is to evaluate if the rapid changes in steatosis and biomarkers consistent with the resolution of observed NASH translates to similar clinically meaningful changes in liver histopathology. Additional correlative analyses will be performed between liver histology and the various

liver imaging studies and exploratory serum biomarkers collected during the study. The results of these data will be used to support the development of non-invasive tools for monitoring treatment. Additionally, these results may also be useful for predicting early response and stopping rules.

6 Study Objectives

The objectives of this study are as follows:

Primary Objective:

- Evaluate the treatment effect of NGM282 on absolute liver fat content as measured by MRI-PDFF in patients with histologically confirmed NASH.

Secondary Objectives:

- Assess the safety and tolerability of NGM282 in patients with NASH with up to 24 weeks of treatment with NGM282.
- Evaluate the percentage change in absolute liver fat content at End of Treatment EOT.
    - In the open-label single-blind cohort, additional evaluations will be performed at 6 and 18 weeks.
    - In the placebo-controlled 24-week histology cohort, additional evaluations will be performed at 6, 24, and 30 weeks.
- Evaluate the percentage of normalization for liver fat content at EOT.
- Evaluate the change in liver fat content response rate as defined by a ≥ 5% decrease in absolute liver fat content.
- Evaluate the absolute and percentage changes from Baseline to EOT as well as the percentage of normalization of the following parameters: ALT, AST, triglycerides, bilirubin (total and direct), and GGT. Percentage of normalization will also be investigated for a clinically meaningful threshold for triglycerides.
- Evaluate the absolute and percentage changes from Baseline to EOT of the following (if collected as part of the cohort):
    - Total cholesterol, HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), triglycerides, and lipoprotein particles
        - In addition, evaluate the absolute and percentage change from Baseline to EOS of the above lipid parameters in the open-label single-blind cohort.
    - [redacted]

  - Fasting blood glucose, insulin levels, [redacted], and homeostasis model assessment–estimated insulin resistance (HOMA-IR)
  - Pro-C3 and ELF score (Placebo Controlled 24 Week Histology Cohort)
  - Body weight, body mass index (BMI), and waist circumference
  - C4 and serum bile acids
  - Bile-mediated absorption as measured by vitamin D, International Normalized Ratio (INR), and fecal fat content

- Evaluate the liver histologic response in Placebo Controlled 24 Week Histology Cohort
  - Improvement in liver fibrosis by ≥ 1 stage by NASH Clinical Research Network (CRN) criteria with no worsening of steatohepatitis
  - Resolution of NASH (defined as an NAS score of 0 or 1 for inflammation and 0 for ballooning) with no worsening of fibrosis as determined by the NASH CRN criteria.
- Evaluate the exposure of NGM282 in patients with NASH.
  - In the double-blind and placebo-controlled 24-week histology cohorts, NGM282 exposure will be compared to placebo at 2 hours post-dose at Day 1 and EOT and pre-dose at all on-treatment study visits.
  - In the open-label single-blind cohort, NGM282 exposure will be evaluated at 2 hours post-dose at Day 1 and EOT and pre-dose at all on-treatment study visits. Additional PK samples will be collected at Baseline and 1, 2, 4, 8, and 12 hours post-dose on Day 1 and Week 6 in a subset of subjects in each dosing group.
  - Exposure of all doses from all cohorts will be compared to each other as well as to exposure in other study populations treated with NGM282 (Studies 12-0101, 13-0102, 13-0103, 14-0104, and 15-0106).
- Evaluate the efficacy and safety of rosuvastatin administered in response to increases in total cholesterol and LDL-C from NGM282 treatment (open-label single-blind and placebo-controlled 24-week histology cohorts only).
- Compare the dose-related changes in the safety, tolerability, PK, and PD parameters within and across the double-blind and open-label single-blind cohorts.

Exploratory Objectives

The exploratory objectives of this study are:

- [redacted]

7 Study Design

This is a multiple-center evaluation of NGM282 in a randomized, double-blind, placebo-controlled, parallel-group cohort with additional open-label single-blind and placebo-controlled 24-week histology cohorts when administered for up to 24 weeks as an SC injection in patients with histologically confirmed NASH.

In the double-blind cohort, approximately 75 patients will be randomized across approximately 20 sites worldwide. Patients to be studied will have histologically confirmed NASH as defined by the NIH NASH Clinical Research Network (Kleiner 2005) and determined by a qualified local pathologist's reading (see Appendix A). Historical biopsy results within 6 months of Screening may be used for inclusion into the study; otherwise, a liver biopsy must be obtained for assessment. Patients must have a NAS of at least 4, with 1 point in each of the three components, along with the presence of fibrosis. Patients with cirrhosis will be excluded from this study. Patients will undergo MRI during the Screening period, which must demonstrate at least 8% total fat content.

On Day 1, patients will be randomized into one of the three treatment arms (NGM282 3 mg, NGM282 6 mg, or placebo) in a 1:1:1 ratio. Patients will be stratified at randomization according to non-diabetic and diabetic status at Day 1 to ensure an even distribution across the three groups. Treatment assignment will be blinded to the sites, study subjects, sponsor, and Medical Monitor throughout the study period. Study-drug self-administration instructions and training will be provided to the subjects and a weekly study-drug kit will be dispensed. The first dose (Day 1) and doses at Weeks 1, 2, 4, 8, and 12 will be self-administered in the clinic, with all other doses through Week 12 self-administered at home. Self-administration should occur in the morning for every dose in both the clinic and at home.

Subjects will return to the clinic on Weeks 1, 2, 4, and 8 for on-treatment assessments and to receive weekly study-drug kits. Week 12 will be the EOT clinic visit. Subjects will return to the clinic at Week 16 (or 4 weeks after last dose) for an EOS follow-up visit. Subjects are

requested to undergo MRI performed during Screening and at Week 1 (EOT) Early Withdrawal visit.

In the open-label single-blind cohort, up to 100 patients (25 per dosing group) will be enrolled from ~6–8 U.S. sites. Subjects will be required to meet enrollment criteria similar to those of the double-blind cohort with the exception of the following, specifically defined in protocol Section 8.1.2: 1) historical biopsy window extended to 12 months; 2) limitations on the use of glucagon-like peptide-1 (GLP1) agonists; 3) glycated hemoglobin (HbA1c) level ≤ 9.5%; 4) LDL levels at Screening need to be ≤ 165 mg/dL; 5) exclusion of specific lipid-lowering therapies prior to and during study period; 6) no contraindications to receiving statins. The single-blind cohort is not randomized. At Day 1 eligible patients will be sequentially enrolled into the study and categorized as either statin-naïve versus statin experienced with no more than 8 statin experienced subjects within each dosing group. Subjects will be enrolled sequentially initially into the dosing Group 1 and enrollment will be continuous within the dosing group. Sequencing of the subsequent 2 dosing groups will be based on PD and safety parameters from dosing Group 1. The subsequent 2 dosing groups may run in parallel. A fourth optional dosing group may be conducted based on the safety/tolerability, imaging data, and histology (dosing Group 3 only) data from the prior 3 dosing groups. Dosing group sequence and individual subject treatment assignment will be blinded only to the study subjects throughout the study period.

The first dose of NGM282 (Day 1) and doses at the Weeks 2, 4, 6, 8, and 12 study visits will be self-administered in the clinic, with all other doses throughout the treatment period self-administered at home. Self-administration of NGM282 should occur in the morning for every dose in both the clinic and at home. Subjects will return to the clinic on Weeks 2, 4, 6, and 8 for on-treatment assessments and to receive weekly NGM282 study-drug kits. LDL-C will be evaluated at Weeks 2, 4, and 8 in all subjects for possible increases in lipid levels associated with NGM282 administration. Rosuvastatin will be started in subjects meeting specific LDL-C level criteria. The specific dosing and administration of rosuvastatin will be based on whether the subject is statin naïve versus statin experienced and LDL-C levels at Weeks 2, 4, and 8. The dosing algorithms are specifically outlined in Section 10.4 of the study protocol. Bottles of rosuvastatin tablets will be dispensed at Weeks 2, 4, and 8, depending on observed lipid levels and dosing algorithm in Section 10.4. Week 12 will be the EOT clinic visit and subjects will return to the clinic at Week 18 (or 6 weeks after last dose) for an EOS follow-up visit. Subjects are required to undergo MRI performed during Screening and at Weeks 6, 12 (EOT)/Early Withdrawal, and 18 (EOS) visits.

Dosing Groups 3 or 4 will have two other assessments performed to assess liver histology in addition to MRI-PDFF. LiverMultiScan™ will be performed during the MRI assessments at the same time as the MRI-PDFF assessments (Screening and Weeks 6, 12, and 18).
An additional post-treatment liver biopsy will be performed at Week 12. The purpose of this biopsy is to assess early changes in liver histopathology (including changes in the NAS,

resolution of NASH, and changes in fibrosis) and compare and correlate to the liver imaging studies and key serum biomarkers collected during the study. The historical liver biopsy window for this subset of subjects will be 3 months prior to Screening. Subjects who wish to participate in the study but do not agree to the second biopsy will be allowed to Screen and enroll for other dosing groups if still open and they meet enrollment criteria. Dosing Group 4 will be initiated only after all subjects in Cohort 3 have been enrolled and a minimum of 10 subjects have completed 12 weeks of treatment in order to do a preliminary review of key data.

In the placebo-controlled 24-week histology cohort, up to 75 subjects (50 active at a single dose of NGM282; 25 placebo) will be enrolled from ~10 U.S. sites and treated for 24 weeks with a 6-week safety follow-up. Subjects will be required to meet enrollment criteria similar to those of the open-label single-blind cohort as specifically defined in protocol Section 8.1.1 with the exception of the following: 1) only subjects with Stages 2 and 3 fibrosis at Screening will be enrolled. At Day 1 eligible subjects will be randomized into the study and stratified as either fibrosis stage 2 or 3. The dose of NGM282 to be studied will be 1 mg based on comparative evaluation of the safety, non-invasive efficacy parameters, and histology from the completed 3 mg 12-week histology dosing group (Group 3) and preliminary data from a subset of subjects from the ongoing 1 mg 12-week histology dosing group (Group 4) in the open-label single-blind cohort. The active dose selection for this cohort will be blinded to the study site and subjects throughout the study period.

The first dose of NGM282 (Day 1) and doses at Weeks 2, 4, 6, 8, 12, 18, and 24 study visits will be self-administered in the clinic, with all other doses throughout the treatment period self-administered at home. Self-administration of NGM282 or placebo should occur as close as possible to the same time each day for every dose. Subjects will return to the clinic on Weeks 2, 4, 6, 8, 12, 18 and 24 for on-treatment assessments and to be dispensed NGM282 or placebo study-drug kits through Week 18. LDL-C (LDL-direct may be used if LDL-C was not able to be analyzed) will be evaluated at Weeks 2, 4, 8, and 12 in all subjects for possible increases in lipid levels associated with NGM282 or placebo administration. Rosuvastatin will be started in subjects meeting specific LDL-C level criteria. The specific dosing and administration of rosuvastatin will be based on whether the subject is statin naïve versus statin experienced and LDL-C levels at Weeks 2, 4, and 8. A decision about possible second-line lipid-lowering therapy with ezetimibe will be made on a case by case basis for subjects that have not achieved an adequate response or are unable to tolerate rosuvastatin. Bottles of rosuvastatin tablets will be dispensed to all subjects initially and instructions to initiate dosing are dependent on observed lipid levels according to the dosing algorithm in Section 10.4. Week 24 will be the EOT clinic visit and subjects will return to the clinic at Week 30 (or 6 weeks after last dose) for an EOS follow-up visit. Subjects are required to undergo MRI performed during Screening and at Weeks 6, 12, 24 (EOT)/Early Withdrawal, and 30 (EOS) visits.

This cohort will have two other assessments performed to assess liver histology in addition to MRI-PDFF. [redacted] An additional post-treatment liver biopsy will be performed at Week 24. The purpose of this biopsy is to assess changes in liver histopathology (including changes in the NAS, resolution of NASH, and changes in fibrosis) and compare and correlate to the liver imaging studies and key serum biomarkers collected during the study.

7.1 Study-Stop Criteria

The entire study or a single dosing arm may be discontinued or not initiated at the discretion of the Sponsor based on the occurrence of the following:

- AEs with respect to their nature, frequency, severity, and/or duration
- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of patients
- Cancellation of drug development

The entire study will be discontinued by the sponsor if there are three or more related Grade 3 or Grade 4 treatment-emergent adverse events (TEAEs) of the same Common Terminology Criteria for Adverse Events (CTCAE) category.

8 Enrollment Criteria

8.1 Double-blind, Open-label Single-blind and Placebo-controlled 24 Week Histology Cohorts

8.1.1 Inclusion Criteria

Patients who meet the following criteria may be included in the study:

1. Males and females between 18 and 75 years of age (except self-identified of Asian descent), able to comprehend and willing to sign an Informed Consent Form (ICF).
2. Histologically confirmed NASH diagnosis as defined by the NIH NASH Clinical Research Network (see Appendix A, Kleiner 2005) and liver biopsy criteria outlined below. A historical biopsy is acceptable if performed within the required time period and tissue slides are available for a qualified pathology read.

   Double-Blind Cohort:

   a. NAS of at least 4 with 1 point in each component
   b. Histologic evidence of fibrosis without cirrhosis
      i. Fibrosis stage 1-3
   c. Liver biopsy within 6 months of Screening.

   Open-Label Single Blind Cohort:

a. NAS of at least 4 with 1 point in each component
b. Histologic evidence of fibrosis without cirrhosis
    i. Fibrosis stage 1-3
c. Liver biopsy within 12 months of Screening.
    i. Dosing Groups 3 or 4 must have a liver biopsy within 3 months of Screening in order to serve as the baseline comparison for the additional EOT biopsy.

Placebo-Controlled 24 Week Histology Cohort:

a. NAS of at least 4 with 1 point in each component
b. Histologic evidence of fibrosis without cirrhosis
    i. Fibrosis stage 2-3
c. Liver biopsy within 3 months of Screening in order to serve as the baseline comparison for the additional EOT biopsy.

3. Total liver fat content of ≥ 8% as measured by MRI-PDFF (MRI may be used for up to 8 weeks from the date of the original scan, including use for re-screened subjects)
4. Insulin-resistant or stable T2D

Double-Blind Cohort:

a. Stable T2D is defined as HbA1c ≤ 8.5% at Screening.
b. Diabetes medications: require a stable regimen for at least 3 months prior to Day 1 and throughout the study.
c. Insulin resistance will be based on fasting insulin level ≥ 10uIU/mL.

Open-Label Single Blind:

a. Stable T2D is defined as HbA1c **≤ 9.5%** at Screening.
b. Diabetes medications (except GLP1 agonists): require a stable regimen for at least 3 months prior to Day 1 and throughout the study.
c. GLP1 agonists: require a stable regimen for at least 12 months prior to Day 1 and throughout study
d. Insulin resistance will be based on fasting insulin level ≥10uIU/mL.

Placebo-Controlled 24 Week Histology Cohort:

Patients with T2D or insulin resistance will be allowed to enroll under the following conditions listed below and patients who do not have T2D or insulin resistance can be enrolled as long as all other criteria are met.

a. HbA1c **≤ 9.0%** at Screening
b. Patients taking diabetes medications (except GLP1 agonists) require a "stable" regimen for at least 3 months prior to Day 1 and throughout study.
    i. GLP1 agonists and pioglitazone: require a stable regimen for at least 12 months prior to Day 1 and throughout the study.

ii. Stable insulin dosing is defined as reasonable dosage adjustments to maintain glucose control.

5. Other therapies for NAFLD or NASH: requires a stable regimen for at least 3 months prior to the Screening biopsy of record and throughout the study. May include vitamin E, milk thistle, thiazolidinediones and pentoxifylline.

   Double-Blind Cohort:

   Includes statins.

   Open-Label Single Blind and Placebo Controlled 24 Week Histology Cohorts:

   Includes statins if the conditions below are met. Other therapies may include vitamin E (> 800 IU Placebo cohort only), milk thistle, thiazolidinediones (open-label, single-blind only) or pentoxifylline.

   a. Patient can be defined as statin naïve or experienced at Screening based on the following definitions:
      i. **Statin-naïve:** no administration of statins within 3 months prior to enrollment.
      ii. **Statin experienced**: administration of ≤ 50% of the maximal dose of current statin therapy.
   b. Requires a stable regimen for at least 3 months prior to Screening through Week 2.

   The following are the acceptable daily doses of approved statin therapies, including combination preparations of statins and other lipid lowering agents. Also listed under Concomitant Medications in Section 9.7.

   - Atorvastatin: ≤ 40 mg/d
   - Fluvastatin: ≤ 40 mg/d
   - Lovastatin: ≤ 40 mg/d (immediate release), ≤ 30 mg/d (extended release)
   - Pitavastatin: ≤ 2 mg/d
   - Pravastatin: ≤ 40 mg/d
   - Rosuvastatin: < 20 mg/d (Note: must be < not ≤ 20 mg/d)
   - Simvastatin: ≤ 40 mg/d

6. The following liver enzyme parameters must be met at Screening:
   a. ALT and AST ≤ 250 IU/L
   b. Abnormal ALT defined as: ≥ 30 IU in males and ≥ 19 IU in females
   d. AST ≥ 30 IU/L except for patients with a historical biopsy within 3 months of screening with NAS of at least 4 with 1 point in each component and fibrosis stage 2 or 3 (Placebo-Controlled Cohort only)

7. The following additional laboratory parameters must also be met at Screening:

a. Total bilirubin must be within normal range. For patients diagnosed with Gibert's Syndrome, please contact medical monitor/designee
b. INR ≤ 1.3 (in the absence of warfarin or other anticoagulant therapy)
c. Creatinine clearance ≥ 90 mL/min as calculated by Cockcroft-Gault equation
d. Alpha fetoprotein (AFP) < 100 ng/mL
e. LDL C ≤ 185 mg/dL (except Double-blind cohort and ≤ 165 mg/dL for the Open-Label Single Blind)
f. LDL-C must also be ≥ 50 mg/dL for **statin naïve** patients (Placebo cohort only)
g. Platelet count must be within normal limits 150-450 K/uL (Placebo-Controlled Cohort only)

8. Female patients must be of non-childbearing potential defined as women who have had a hysterectomy, bilateral oophorectomy, medically documented ovarian failure, or are documented postmenopausal (follicle stimulating hormone > 40 mIU/mL).
9. Female patients of childbearing potential defined as including women < 55 years of age with 2 years of amenorrhea (absence of menstruation) must have a negative serum pregnancy test at Screening and urine pregnancy test at the Day 1 visit prior to dosing.
10. Female patients of childbearing potential and male patients with a female partner of childbearing potential must agree to consistent and adequate birth control from Screening to 30 days after the last dose of study medication.

    One of the following forms of contraception is required and male patients must also use a condom.

    a. Hormone-containing contraceptive
    b. Intrauterine device with a failure rate < 1% per year
    c. Cervical cap or diaphragm with spermicidal agent
    d. Sterilization (tubal ligation or vasectomy)
11. Able and willing to comply with the dosing instructions for study-drug administration and able to complete the study schedule of assessments.

8.1.2 Exclusion Criteria

The following criteria will exclude patients from the study:

1. Clinically significant acute or chronic liver disease of an etiology other than NASH
2. Evidence of drug-induced steatohepatitis secondary to amiodarone, corticosteroids, estrogens, methotrexate, tetracycline, or other medications known to cause hepatic steatosis
3. History or presence of cirrhosis (compensated or decompensated) as determined by histology, relevant medical complications, and/or laboratory parameters

4. Prior liver transplantation
5. Any acute cardiovascular event (e.g. myocardial infarction, stroke, severe arrhythmia or hospitalization for any cardiac related event) or evidence of active cardiovascular disease within 6 months of Screening
6. History of bypass or bariatric surgery or planned procedure during the study period. Removal of a gastric balloon or lap band is permitted if surgery performed within 6 months prior to Day 1.
7. Type 1 diabetes
8. History of clinically significant unstable or untreated illness or any other major medical disorder that may interfere with patient treatment, assessment, or compliance with the protocol
9. Any contraindication or inability to obtain an MRI
10. Inability to obtain or any contraindication to liver biopsy (if a historical biopsy with viable tissue slides are not available within the required time period)
11. Screening ECG with clinically significant abnormalities as determined by the Investigator
12. Positive for HBsAg, anti-HIV, or anti-HCV plus HCV-RNA. Patients who are anti-HCV positive but HCV-RNA negative (secondary to treatment or viral clearance) are eligible as long as there is evidence of viral negativity for a minimum of 12 weeks.
13. History of malignancy diagnosed or treated within 2 years (recent localized treatment of squamous or non-invasive basal cell skin cancers is permitted; cervical carcinoma in situ is allowed if appropriately treated prior to Screening); patients under evaluation for malignancy are not eligible.
14. Clinically-relevant drug or alcohol abuse within 12 months of screening. A positive drug screen will exclude patients unless it can be explained by a prescribed medication; the diagnosis and prescription must be approved and documented as such by the Investigator.
15. Use of any prohibited concomitant medications as described in Section 9.7 prior to Day1.
16. Prior participation in a clinical trial of NGM282

    Double Blind Cohort:

    Prior participation in a clinical trial of NGM282 is excluded.

    Open Label Single Blind and Placebo Controlled 24 Week Histology Cohorts:

    Prior participation in a clinical trial of NGM282 is excluded **unless** previously enrolled into a placebo arm of the trial.

17. Patient with severe allergic or anaphylactic reactions to recombinant therapeutic proteins, fusion proteins, or chimeric, human, or humanized antibodies.
18. Participation in a study of another investigational agent within 28 days or five half-lives of the drug (whichever is longer) prior to Screening

19. Any acute or chronic condition that, in the opinion of the Investigator, would limit the patient's ability to complete and/or participate in this clinical study.
20. Pregnancy or lactation
21. Use of ezetimibe, colesevelam, cholestyramine, niacin, PCSK9 inhibitors, or other lipid-lowering agents within 3 months of Screening (except Double-blind cohort).

    Placebo-Controlled 24 Week Histology Cohort Only

    Use of any other lipid lowering agents or combination preparation of statins **except** ezetimibe when approved by MM/designee as second line lipid management therapy, within 3 months of Screening and throughout study

    a. colesevelam, cholestyramine, niacin, PCSK9 inhibitors (evolocumab or alirocumab), colestid, fibrates, fenofibrates, pharmacologic/prescribed fish oil
22. History or presence of ALT elevations or significant side effects indicative of statin intolerance (except Double-blind cohort).
23. Use of weight loss medications including: orlistat, phentermine, topiramate, qsymia, lorcaserin hydrochloride, naltrexone hydrochloride, liraglutide (use is for weight loss not T2D, e.g. Saxenda®), benzphentamine, diethylpropion and phendimetrazine, within 3 months of screening and throughout study

Additionally for all cohorts, the Investigator has discretion to repeat assessments if he/she believes there is a good chance the results were spurious and do not accurately represent the patient's true values. Repeat assessments must be conducted within the Screening Period.

8.2 Discontinuation of Study Treatment for an Individual Subject

Study treatment will be discontinued if any of the following CTCAE categories are observed:

- Any related Grade 3 TEAE
- Any Grade 4 or higher TEAE

Additionally, subjects will be evaluated for possible discontinuation if the following changes in liver-related laboratory parameters are observed:

- Elevation of ALT > 2x above subject-specific baseline value (calculated using the median of the Screening and Day 1 value) and total bilirubin > 2x ULN:
  - ALT, AST, and total bilirubin must be re-tested within 72 hours.
  - Subjects with persistent elevations above the defined thresholds should be evaluated for discontinuation of study drug(s), independent of whether they are symptomatic or not.
- Elevation of only ALT > 2x above subject-specific baseline:
  - ALT, AST, and total bilirubin must be re-tested within 72 hours.

- Subjects with persistent elevations above the defined thresholds who are *symptomatic* should be evaluated for discontinuation of study drug(s).
- Subjects with persistent elevations above the defined thresholds who are *asymptomatic* may continue treatment under protocol-defined close observation criteria.
- Subjects continuing treatment under *close observation* should implement study procedures and assessments as part of the study conduct:
    1. Repeat liver enzyme and serum bilirubin tests two or three times weekly. The frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.
    2. Repeat additional tests to evaluate liver synthetic function (e.g., INR, direct bilirubin) as appropriate.
    3. Obtain a detailed history of symptoms and prior or concurrent diseases.
    4. Obtain a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, environmental toxin exposure, and special diets.
    5. Rule out acute viral hepatitis and other acute or chronic hepatobiliary diseases.

For the double-blind cohort, dose reductions will be allowed on a case by case basis for subjects receiving 6 mg or matched 6 mg placebo for safety or tolerability, but must be approved by the Medical Monitor. If approved, the subject will be decreased to 3 mg or the matched 3 mg placebo to be aligned with whether they were initially receiving active drug or placebo prior to the dose reduction. Subjects receiving 3 mg or matched 3 mg placebo will not be allowed to dose-reduce during the study period.

For the open-label single-blind cohort, no dose reductions will be allowed.

For the placebo-controlled 24-week histology cohort **no dose reductions** will be allowed. Additionally, ALT, AST, and all lipid laboratory results are blinded starting with Week 2 onward. The Medical Monitor will be reviewing and monitoring all laboratory results and if any of the liver related testing parameters are observed, investigators will be notified immediately to discuss further evaluation.

8.3 Discontinuation of Subjects from Study Participation

Subjects will be informed that they are free to withdraw from the study at any time and for any reason. The Principal Investigator (PI) may remove a subject from the study if, in the PI's opinion, it is not in the best interest of the subject to continue the study. Subjects may be discontinued due to a change in compliance with an inclusion/exclusion criterion that is clinically relevant and affects subject safety, occurrence of AEs, occurrence of pregnancy, or

administration of non-permitted concomitant medication that might affect subject safety or study assessments/objectives. Notification of discontinuation will be made immediately to the Sponsor's Medical Monitor. In case of premature discontinuation of study participation, efforts will be made to perform all final EOT and EOS visits/assessments. The date the subject is withdrawn from the study and the reason for discontinuation will be recorded on the subject's Case Report Form (CRF). All withdrawn subjects will be followed until resolution of any AEs or until any unresolved AEs are judged by the PI to have stabilized.

9 Study Methods

9.1 Schedule of Study Procedures for Double-blind Cohort

The Schedule of Study Procedures for the double-blind cohort is shown in Table 2. The visits should occur as close to the intended dates as possible. However, there is an acceptable ± 3 day window for individual scheduled visits. Subjects attending any visits out of windows from Day 1 to Week 12/Early Withdrawal (EOT) visit should be brought back into compliance with the overall study-visit schedule as soon as possible thereafter. Subjects will then return to the clinic at Week 16 (or 4 weeks after last dose) for an EOS follow-up visit.

The Investigator has discretion to repeat assessments if he/she believes the results do not accurately represent the patient's true values. Repeat assessments must be conducted within the 4-week (±5 days) Screening Period.

Table 2. Schedule of Study Procedures for Double-Blind Cohort

Study Procedure	Days –28 to –1 (Screening) [a]	Day 1	Wk 1	Wk 2	Wk 4	Wk 8	Wk 12 (EOT)/ EW	Wk 16 (EOS)
Informed consent	X							
Demographics	X							
Medical history	X							
Inclusion/exclusion criteria	X	X						
Height	X							
Body weight, BMI, waist circumference	X	X					X	X
Physical exam	X	X		X	X	X	X	X
12-lead ECG	X	X		X			X	X
Vital signs	X	X	X	X	X	X	X	X
Liver biopsy [b] (or tissue slides)	X							
MRI [c]	X						X	
Prior and concomitant medications	X	X	X	X	X	X	X	X
Randomization		X						
Study drug self-administration training		X	X	X	X			
Dispense study drug		X	X	X	X	X		
Medication compliance			X	X	X	X	X	
Adverse event (AE) evaluations		X	X	X	X	X	X	X
LISSA evaluations [d]		X	X	X	X	X	X	X
PK blood samples [e]		X	X	X	X	X	X	X
Chemistry [fasted ≥ 10 hours]	X	X	X	X	X	X	X	X
Complete blood count (CBC)	X	X	X	X	X	X	X	X
Urinalysis (UA)	X	X			X		X	X
Fasting lipid panel		X			X		X	
Lipoprotein particles		X					X	
[redacted]		[redacted]					[redacted]	
HbA1c	X	X					X	
Insulin level and HOMA-IR	X	X					X	
Stool sample		X					X	
Hepatitis and HIV screen	X							
Urine drug screen	X							

Table 2. Schedule of Study Procedures for Double-Blind Cohort (cont'd)

Study Procedure	Days –28 to –1 (Screening) [a]	Day 1	Wk 1	Wk 2	Wk 4	Wk 8	Wk 12 (EOT)/ EW	Wk 16 (EOS)
Pregnancy test [f]	X	X					X	X
C4 and serum bile acids		X					X	
Alpha fetoprotein	X							
Vitamin D		X					X	X
International Normalized Ratio	X	X					X	X
[redacted]		[redacted]			[redacted]		[redacted]	[redacted]
Cytokines (IL-6, TGF-β)		X			X		X	
[redacted]		[redacted]					[redacted]	
Anti-drug antibodies		X		X	X	X	X	X
Neutralizing antibodies		X		X	X	X	X	X
Exploratory biomarkers		X					X	

AE = adverse event; BMI = body mass index; C4 = 7-alpha-hydroxy-4-cholesten-3-one; CBC = complete blood count; ECG = electrocardiogram; EOS = End of Study; EOT = End of Treatment; EW = Early Withdrawal; [redacted] HIV = human immunodeficiency virus; HOMA-IR = homeostasis model assessment–estimated insulin resistance; [redacted]; IL-6 = interleukin 6; LISSA = local injection-site symptom assessment; [redacted]; MRI = magnetic resonance imaging; MRI-PDFF = magnetic resonance imaging–proton density fat fraction; PK = pharmacokinetic; TGF-β = transforming growth factor beta; UA = urinalysis; Wk = week.

[a] There must be a minimum of 14 days between Screening and Day 1 visits for adequate separation of the repeated Chemistry (liver function tests) and International Normalized Ratio assessments.

[b] Liver biopsy will be performed only in patients who do not have a biopsy available within 6 months of Screening.

[c] Screening MRI-PDFF result will serve as Baseline for efficacy endpoint analysis. Adiposity assessments will be collected as part of the standard MRI procedure at all sites. [redacted]

[d] LISSA evaluations will be performed pre- and post-dose for all on-treatment visits. At Week 16, a single LISSA will be performed to assess prior-dose injection-site reactions.

[e] PK blood samples will be collected before subjects dose themselves in the clinic (pre-dose). At Day 1 and Week 12, an additional PK blood sample will be collected 2 hours post-dose.

[f] A serum pregnancy test will be performed on all female subjects at Screening, Week 12, and Week 16. A urine pregnancy test will be performed on all female subjects at Day 1 (pre-dose).

9.2 Study Visit Procedures for Double-blind cohort

9.2.1 Day –28 to Day –1 (Screening) Procedures

Subjects will report to this visit fasted. The following screening procedures will be performed for all potential subjects at a visit (or visits) conducted within 28 days prior to dosing:

- Obtain informed consent.
- Collect demographic data.
- Ascertain medical history.
- Assess inclusion/exclusion criteria.
- Measure height.
- Measure body weight, BMI, and waist circumference.
- Conduct physical examination.
- Obtain 12-lead ECG (after subject has been supine for at least 5 minutes).
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Obtain MRI (prior to any histologic evaluation).
- Obtain viable tissue slides from eligible historical liver biopsy or undergo a liver biopsy procedure to obtain new tissue.
- Record prior and concomitant medications.
- Obtain 10-hour fasted clinical laboratory samples for the following:
    - Chemistry
    - Complete blood count (CBC)
    - HbA1c
    - Insulin
    - HOMA-IR calculation
    - INR
    - AFP
    - Serum pregnancy test (all female subjects)
- Obtain clinical laboratory samples for HIV antibody and hepatitis screen.
- Obtain urine samples for the following:
    - Urinalysis (UA)
    - Selected drugs of abuse

9.2.2 Day 1 Procedures

Subjects will report to this visit fasted. The Day 1 visit should be a minimum of 14 days from the Screening visit in order to allow for adequate separation of the repeated Chemistry (liver function tests) and INR assessments. The following procedures will be performed at the Day 1 Visit:

Pre-dose:

- Reassess inclusion/exclusion criteria.
- Measure body weight, BMI, and waist circumference.
- Conduct physical examination.
- Obtain 12-lead ECG (after subject has been supine for at least 5 minutes).
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Record concomitant medications.
- Record AEs.
- Obtain 10-hour fasted clinical laboratory samples for the following:
    - Chemistry
    - CBC
    - Lipid panel
    - Lipoprotein particles
    - [redacted]
    - HbA1c
    - Insulin
    - HOMA-IR calculation
    - C4 and serum bile acids
    - Vitamin D
    - INR
    - [redacted]
    - Cytokines
    - [redacted]
    - PK (pre-dose)
    - Anti-drug antibodies (ADAs)
    - Neutralizing antibodies (NAbs)
    - Exploratory biomarkers
- Obtain stool sample for microbiome and fecal fat assessment.
- Obtain urine samples for the following:
    - Pregnancy test
    - UA

In-clinic dosing:

- Confirm inclusion/exclusion criteria and no change in clinical symptoms or other evidence of a significant change in liver function from Screening.
- Perform randomization.
- Dispense initial study-drug kit/diary (for recording of date/time of study-drug dosing).

- Provide study-drug self-administration training.
- Oversee subject's study-drug self-administration.

Before clinic discharge:

- Obtain 2-hour post-dose PK sample.
- Record AEs.
- Perform local injection-site symptom assessment (LISSA) evaluation.
- Schedule subject for Week 1 visit.

9.2.3 Week 1 Procedures

Subjects will report to this visit fasted and not dosed with NGM282. The following procedures will be performed at the Week 1 visit:

Pre-dose:

- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Record concomitant medications.
- Record AEs.
- Perform LISSA evaluation.
- Obtain 10-hour fasted clinical laboratory samples for the following:
    - Chemistry
    - CBC
    - PK (pre-dose)

In-clinic dosing:

- Collect old study-drug kit/diary and conduct reconciliation.
- Dispense new study-drug kit/diary.
- Oversee subject's study-drug self-administration (from new kit).

Before clinic discharge (20 minutes after dosing):

- Record AEs.
- Perform LISSA evaluation.
- Schedule subject for Week 2 visit.

9.2.4 Week 2 Procedures

Subjects will report to this visit fasted and not dosed with NGM282. The following procedures will be performed at the Week 2 visit:

Pre-dose:

- Conduct physical examination.
- Obtain 12-lead ECG (after subject has been supine for at least 5 minutes).
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Record concomitant medications.
- Record AEs.
- Obtain 10-hour fasted clinical laboratory samples for the following:
    - Chemistry
    - CBC
    - PK (pre-dose)
    - ADAs
    - NAbs
- Perform LISSA evaluation.

In-clinic dosing:

- Collect old study-drug kit/diary and conduct reconciliation.
- Dispense new study-drug kit/diary.
- Oversee subject's study-drug self-administration (from new kit).

Before clinic discharge (20 minutes after dosing):

- Record AEs.
- Perform LISSA evaluation.
- Schedule subject for Week 4 visit.

9.2.5 Week 4 Procedures

Subjects will report to this visit fasted and not dosed with NGM282. The following procedures will be performed at the Week 4 visit:

Pre-dose:

- Conduct physical examination.
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Record concomitant medications.

- Record AEs.
- Obtain 10-hour fasted clinical laboratory samples for the following:
  - Chemistry
  - CBC
  - Lipid panel
  - [redacted]
  - Cytokines
  - PK (pre-dose)
  - ADAs
  - NAbs
- Obtain urine samples for UA.

In-clinic dosing:
- Collect old study-drug kit/diary and conduct reconciliation.
- Dispense new study-drug kit/diary.
- Oversee subject's study-drug self-administration (from new kit).

Before clinic discharge (20 minutes after dosing):
- Record AEs.
- Perform LISSA evaluation.
- Schedule subject for Week 8 visit.

9.2.6 Week 8 Procedures

Subjects will report to this visit fasted and not dosed with NGM282. The following procedures will be performed at the Week 8 visit:

Pre-dose:
- Conduct physical exam.
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Record concomitant medications.
- Record AEs.
- Perform LISSA evaluation.
- Obtain 10-hour fasted clinical laboratory samples for the following:
  - Chemistry
  - CBC
  - PK (pre-dose)
  - ADAs
  - NAbs

In-clinic dosing:

- Collect old study-drug kit/diary and conduct reconciliation.
- Dispense new study-drug kit/diary.
- Oversee subject's study-drug self-administration (from new kit).

Before clinic discharge (20 minutes after dosing):

- Record AEs.
- Perform LISSA evaluation.
- Schedule subject for Week 12 (End of Treatment) visit.

9.2.7 Week 12 (End of Treatment)/Early Withdrawal Procedures

Subjects will report to this visit fasted and not dosed with NGM282. The following procedures will be performed at the Week 12/Early Withdrawal Visit:

Pre-dose:

- Measure body weight, BMI, and waist circumference.
- Conduct physical examination.
- Obtain 12-lead ECG (after subject has been supine for at least 5 minutes).
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Obtain a MRI examination.
- Record concomitant medications.
- Record AEs.
- Obtain 10-hour fasted clinical laboratory samples for the following:
    - Chemistry
    - CBC
    - Lipid panel
    - Lipoprotein particles
    - [redacted]
    - C4 and serum bile acids
    - Vitamin D
    - HbA1c
    - Insulin level
    - HOMA-IR calculation
    - INR
    - [redacted]
    - Cytokines
    - [redacted]

  - Serum pregnancy test (all female subjects)
  - PK (pre-dose)
  - ADAs
  - NAbs
  - Exploratory biomarkers

- Obtain stool sample for microbiome and fecal fat assessment.
- Obtain urine sample for UA.
- Perform LISSA evaluation.

In-clinic dosing:
- Collect old study-drug kit/diary and conduct reconciliation.
- Oversee subject's study-drug self-administration (from old kit) (not applicable for Early Withdrawal subjects).

Before clinic discharge (and approximately 20 minutes after dosing):
- Obtain 2-hour post-dose PK sample.
- Record AEs.
- Perform LISSA evaluation.
- Schedule subject for Day Week 16 (End of Study) Visit.

(NOTE: Before-clinic-discharge assessments [PK sampling, AE recording, and LISSA evaluation] are not applicable for Early Withdrawal subjects. However, Early Withdrawal subjects should be scheduled for a 4-week Follow-up Visit.)

9.2.8 Week 16 (End of Study) Procedures

This visit will be performed 4 weeks after the last dose of study medication. Subjects will report to this visit fasted. The following procedures will be performed at the Week 16 visit:

- Measure body weight, BMI, and waist circumference.
- Conduct physical examination.
- Obtain 12-lead ECG (after subject has been supine for at least 5 minutes).
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Record concomitant medications.
- Record AEs.
- Obtain 10-hour fasted clinical laboratory samples for the following:
  - Chemistry
  - CBC

  - PK
  - Vitamin D
  - INR
  - [redacted]
  - Serum pregnancy test (all female subjects)
  - ADAs
  - NAbs

- Obtain urine sample for UA.
- Perform LISSA evaluation.

9.3 Schedule of Study Procedures for Open-label Single-blind Cohort

The Schedule of Study Procedures for the open-label single-blind cohort is shown in Table 3. The visits should occur as close to the intended dates as possible. However, there is an acceptable ± 3-day window for individual scheduled visits. Subjects attending any visits out of windows from Day 1 to Week 12/Early Withdrawal (EOT) visit should be brought back into compliance with the overall study-visit schedule as soon as possible thereafter. Subjects will then return to the clinic at Week 18 (or 6 weeks after last dose) for an EOS follow-up visit.

The Investigator has discretion to repeat assessments if he/she believes the results do not accurately represent the patient's true values. Repeat assessments must be conducted within the Screening Period.

Table 3. Schedule of Study Procedures for Open-Label Single-Blind Cohort

Study Procedure	Days –28 to –1 (Screening) [a]	Day 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12 (EOT) /EW	Wk 18 (EOS)
Informed consent	X							
Demographics	X							
Medical history	X							
Inclusion/exclusion criteria	X	X						
Height	X							
Body weight, BMI, waist circumference	X	X					X	X
Physical exam	X	X	X	X	X	X	X	X
12-lead ECG	X	X			X		X	X
Vital signs	X	X	X	X	X	X	X	X
MRI [b]	X				X		X	X
[redacted]	[redacted]				[redacted]		[redacted]	[redacted]
Liver biopsy [d]	X						X[c]	
IWRS screening registration	X							
IWRS enrollment registration		X						
Prior and concomitant medications	X	X	X	X	X	X	X	X
Adverse event (AE) evaluations		X	X	X	X	X	X	X
LISSA evaluations [e]		X	X	X	X	X	X	X
Chemistry [fasted ≥ 10 hours]	X	X	X	X	X	X	X	X
Complete blood count (CBC)	X	X	X	X	X	X	X	X
HbA1c	X	X					X	X
Insulin level and HOMA-IR	X	X					X	X
[redacted]		[redacted]					[redacted]	[redacted]
International Normalized Ratio (INR)	X	X					X	X
Alpha fetoprotein (AFP)	X							
Pregnancy test [f]	X	X					X	X
Hepatitis and HIV screen	X							
Urinalysis (UA)	X	X			X		X	X
Urine drug screen	X							
Fasting lipid panel	X	X	X	X	X	X	X	X
Lipoprotein particles		X			X		X	X
[redacted]		[redacted]					[redacted]	[redacted]
Lipase		X		X	X	X	X	X
Stool sample		X					X	

Table 3. Schedule of Study Procedures for Open-label Single-blind Cohort (cont'd)

Study Procedure	Days –28 to –1 (Screening) [a]	Day 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12 (EOT) /EW	Wk 18 (EOS)
C4 and serum bile acids		X			X		X	X
Vitamin D		X					X	X
[redacted]		[redacted]			[redacted]		[redacted]	[redacted]
Cytokines (IL-6, TGF-β)		X			X		X	X
PK blood samples [g]		X	X	X	X	X	X	X
Anti-drug antibodies (ADAs)		X	X	X	X	X	X	X
Neutralizing antibodies (NAbs)		X	X	X	X	X	X	X
ELF Panel		X			X		X	X
[redacted]		[redacted]			[redacted]		[redacted]	[redacted]
[redacted]		[redacted]			[redacted]		[redacted]	[redacted]
[redacted]		[redacted]			[redacted]		[redacted]	[redacted]
[redacted]		[redacted]			[redacted]		[redacted]	[redacted]
NGM282 in-clinic self-administration		X	X	X	X	X	X	
Dispense NGM282		X	X	X	X	X		
Dispense rosuvastatin [h]			X	X		X	X	
Medication compliance [i]			X	X	X	X	X	X
Lipid-Lowering Therapy Assessment			X	X		X		

ADA = anti-drug antibody; AE = adverse event; AFP = alpha fetoprotein; BMI = body mass index; C4 = 7-alpha-hydroxy-4-cholesten-3-one; CBC = complete blood count; ECG = electrocardiogram; ELF = enhanced liver fibrosis; EOS = End of Study; EOT = End of Treatment; EW = Early Withdrawal; FFA = free fatty acid; HIV = human immunodeficiency virus; HOMA-IR = homeostasis model assessment–estimated insulin resistance; hs-CRP = high-sensitivity C-reactive protein; IL-6 = interleukin 6; INR = International Normalized Ratio; IWRS = Interactive Voice/Web Response System; LISSA = local injection-site symptom assessment; [redacted]; MRI = magnetic resonance imaging; NAb = neutralizing antibody; PK = pharmacokinetic; TGF-β = transforming growth factor beta; UA = urinalysis; Wk = week.

[a] There must be a minimum of 14 days between Screening and Day 1 visits for adequate separation of the repeated Chemistry (liver function tests) and International Normalized Ratio assessments.

[b] Screening MRI will serve as baseline for efficacy endpoint analysis. Adiposity assessments will be collected as part of the standard MRI procedure at all sites. MRE will be performed at sites with available technology.

[c] [redacted]

[d] All subjects are required to have a liver biopsy result at Screening and subjects in the dosing Groups 3 or 4 will have an additional liver biopsy at Week 12. A Screening liver biopsy will be performed only in subjects who do not have a biopsy available within 12 months of Screening for dosing Groups 1 and 2. For dosing Groups 3 or 4, the liver biopsy must be performed within 3 months of Screening to serve as the Baseline comparison for the additional Week 12 biopsy.

[e] LISSA evaluations will be performed pre- and post-dose for all on-treatment visits. At Week 18, a single LISSA will be performed to assess prior-dose injection-site reactions.

[f] A serum pregnancy test will be performed on all female subjects at Screening, Week 12, and Week 18. A urine pregnancy test will be performed on all female subjects at Day 1 (pre-dose).

[g] PK blood samples will be collected in all subjects before dosing themselves in the clinic (pre-dose) and at 2 hours post-dose at Day 1 and Week 12. In a subset of subjects, PK samples will be collected at pre-dose and 1, 2, 4, 8, and 12 hours after dosing at Day 1 and Week 6.

[h] Rosuvastatin will be dispensed at Weeks 2, 4, and 8 visits based on their LDL-C levels and whether they are statin-naïve versus statin experienced therapy. Subjects on a statin at screening will be dispensed additional rosuvastatin and continue through Week 18.

[i] Medication compliance will be assessed at Week 18 only in subjects who were statin-experienced at Baseline.

9.4 Study Visit Procedures for Open-label cohort

9.4.1 Day –28 to Day –1 (Screening) Procedures

Subjects will report to this visit fasted. The following screening procedures will be performed for all potential subjects at a visit (or visits) conducted within 28 days prior to dosing:

- Obtain informed consent.
- Collect demographic data.
- Ascertain medical history.
- Assess inclusion/exclusion criteria.
- Measure height.
- Measure body weight, BMI, and waist circumference.
- Conduct physical examination.
- Obtain 12-lead ECG (after subject has been supine for at least 5 minutes).
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Obtain an MRI assessment (preferably prior to any histologic evaluation unless a historical biopsy is available).
- Obtain a LiverMultiScan^{TM} reading (dosing Groups 3 or 4 only).
- Obtain viable tissue slides from eligible historical liver biopsy or undergo a liver biopsy procedure to obtain new tissue.
- Conduct Interactive Web Response System (IWRS) screening registration.
- Record prior and concomitant medications.
- Obtain 10-hour fasted clinical laboratory samples for the following:
    - Chemistry
    - CBC
    - Lipid panel
    - HbA1c
    - Insulin
    - HOMA-IR calculation
    - INR
    - AFP
    - Serum pregnancy test (all female subjects)
- Obtain clinical laboratory samples for HIV antibody and hepatitis screen.
- Obtain urine samples for the following:
    - UA
    - Selected drugs of abuse

9.4.2 Day 1 Procedures

Subjects will report to this visit fasted. The Day 1 visit should be a minimum of 14 days from the Screening visit in order to allow for adequate separation of the repeated Chemistry (liver function tests) and INR assessments. The following procedures will be performed at the Day 1 Visit:

Pre-dose:

- Reassess inclusion/exclusion criteria.
- Measure body weight, BMI, and waist circumference.
- Conduct physical examination.
- Obtain 12-lead ECG (after subject has been supine for at least 5 minutes).
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Record concomitant medications.
- Record AEs.
- Perform LISSA evaluation.
- Obtain 10-hour fasted clinical laboratory samples for the following:
  - Chemistry
  - CBC
  - HbA1c
  - Insulin
  - HOMA-IR calculation
  - [redacted]
  - Lipid panel
  - Lipoprotein particles
  - [redacted]
  - Lipase
  - C4 and serum bile acids
  - Vitamin D
  - INR
  - [redacted]
  - Cytokines
  - PK (pre-dose)
  - ADAs
  - NAbs
  - Exploratory biomarker #1
  - Exploratory biomarker #2
  - Enhanced liver fibrosis (ELF) panel

- [redacted]

- Obtain stool sample for microbiome and fecal fat assessment.
- Obtain urine samples for the following:
  - Pregnancy test
  - UA

In-clinic dosing and assessments:

- Confirm inclusion/exclusion criteria and no change in clinical symptoms or other evidence of a significant change in liver function from Screening.
- Confirm no new medications have been started or dose changes of medications during Screening
- Register subject in IWRS for study-drug kit assignment.
- Dispense initial NGM282 study-drug kit/diary (for recording of date/time of study-drug dosing).
- Provide NGM282 study-drug self-administration training.
- Oversee subject's NGM282 study-drug self-administration.
- In a subset of subjects, PK samples will be collected at pre-dose and 1, 2, 4, 8, and 12 hours after dosing.

Before clinic discharge (and approximately 20 minutes after dosing:

- Obtain 2-hour post-dose PK sample (only in subjects **not** participating in the PK sub-study).
- Record new AEs after NGM282 dosing.
- Perform LISSA evaluation.
- Schedule subject for Week 2 visit.

9.4.3 Week 2 Procedures

Subjects will report to this visit fasted and not dosed with NGM282. The following procedures will be performed at the Week 2 visit:

Pre-dose:

- Conduct physical examination.
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Record concomitant medications.
- Record AEs.
- Perform LISSA evaluation.

- Obtain 10-hour fasted clinical laboratory samples for the following:
  - Chemistry
  - CBC
  - Lipid panel
  - PK (pre-dose)
  - ADAs
  - NAbs

In-clinic dosing and dispensing:
- Collect old NGM282 study-drug kit/diary and conduct reconciliation.
- Dispense new NGM282 study-drug kit/diary
- Dispense new rosuvastatin study drug (if indicated as outlined in Section 10.4)
- Oversee subject's NGM282 study-drug self-administration (from new kit).

Before clinic discharge (and approximately 20 minutes after dosing):
- Record new AEs after NGM282 dosing.
- Perform LISSA evaluation.
- Schedule subject for Week 4 visit.

Lipid-Lowering Therapy Assessment:
- Evaluate LDL-C level from Week 2 visit when available.
- Based on the Week 2 LDL-C level, initiate/switch rosuvastatin therapy as outlined in Section 10.4 of the study protocol. The subject should be called by the study site personnel to instruct on the specific administration of the rosuvastatin therapy.

9.4.4 Week 4 Procedures

Subjects will report to this visit fasted and not dosed with NGM282. The following procedures will be performed at the Week 4 visit:

Pre-dose:
- Conduct physical examination.
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Record concomitant medications.
- Record AEs.
- Perform LISSA evaluation.
- Obtain 10-hour fasted clinical laboratory samples for the following:
  - Chemistry

- CBC
- Lipid panel
- Lipase
- PK (pre-dose)
- ADAs
- NAbs

In-clinic dosing and dispensing:

- Collect old NGM282 study-drug kit/diary and conduct reconciliation.
- Collect old rosuvastatin bottle and conduct reconciliation.
- Dispense new NGM282 study-drug kit/diary
- Dispense new rosuvastatin study drug.
- Oversee subject's NGM282 study-drug self-administration (from new kit).

Before clinic discharge (and approximately 20 minutes after dosing):

- Record new AEs after NGM282 dosing.
- Perform LISSA evaluation.
- Schedule subject for Week 6 visit.

Lipid-Lowering Therapy Assessment:

- Evaluate LDL-C level from Week 4 visit when available.
- Based on the Week 4 LDL-C level, initiate/switch/continue/dose increase rosuvastatin therapy as outlined in Section 10.4 of the study protocol. The subject should be called by the study site personnel to instruct on the specific administration of the rosuvastatin therapy.

9.4.5 Week 6 Procedures

Subjects will report to this visit fasted and not dosed with NGM282. The following procedures will be performed at the Week 6 visit:

Pre-dose:

- Conduct physical examination.
- Obtain 12-lead ECG (after subject has been supine for at least 5 minutes).
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Obtain an MRI assessment (preferably prior to any histologic evaluation unless a historical biopsy is available).
- Obtain a LiverMultiScan™ reading (dosing Groups 3 or 4 only).
- Record concomitant medications.

- Record AEs.
- Perform LISSA evaluation.
- Obtain 10-hour fasted clinical laboratory samples for the following:
  - Chemistry
  - CBC
  - Lipid panel
  - Lipoprotein particles
  - Lipase
  - C4 and serum bile acids
  - [redacted]
  - Cytokines
  - PK (pre-dose)
  - ADAs
  - NAbs
  - Exploratory biomarker #1
  - Exploratory biomarker #2
  - ELF panel
  - [redacted]
  - [redacted]
- Obtain urine samples for UA.

In-clinic dosing and dispensing:

- Collect old NGM282 study-drug kit/diary and conduct reconciliation.
- Dispense new NGM 282 study-drug kit/diary.
- Oversee subject's NGM282 study-drug self-administration (from new kit).

Before clinic discharge (and approximately 20 minutes after dosing):

- Record new AEs after NGM282 dosing.
- Perform LISSA evaluation.
- In a subset of subjects, PK samples will be collected at pre-dose and 1, 2, 4, 8, and 12 hours after dosing.
- Schedule subject for Week 8 visit.

9.4.6 Week 8 Procedures

Subjects will report to this visit fasted and not dosed with NGM282. The following procedures will be performed at the Week 8 visit:

Pre-dose:

- Conduct physical exam.
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Record concomitant medications.
- Record AEs.
- Perform LISSA evaluation.
- Obtain 10-hour fasted clinical laboratory samples for the following:
    - Chemistry
    - CBC
    - Lipid panel
    - Lipase
    - PK (pre-dose)
    - ADAs
    - NAbs

In-clinic dosing and dispensing:

- Collect old NGM282 study-drug kit/diary and conduct reconciliation.
- Collect old rosuvastatin study-drug and conduct reconciliation.
- Dispense new NGM282 study-drug kit/diary
- Dispense new rosuvastatin study-drug.
- Oversee subject's NGM282 study-drug self-administration (from new kit).

Before clinic discharge (and approximately 20 minutes after dosing):

- Record new AEs after NGM282 dosing.
- Perform LISSA evaluation.
- Schedule subject for Week 12 (End of Treatment) visit.

Lipid-Lowering Therapy Assessment:

- Evaluate LDL-C level from Week 8 visit when available.
- Based on the Week 8 LDL-C level, initiate/switch/continue/dose increase rosuvastatin therapy as outlined in Section 10.4 of the study protocol. The subject should be called by the study site personnel to instruct on the specific administration of the rosuvastatin therapy.

9.4.7 Week 12 (End of Treatment)/Early Withdrawal Procedures

Subjects will report to this visit fasted and not dosed with NGM282. The following procedures will be performed at the Week 12/Early Withdrawal Visit:

Pre-dose:

- Measure body weight, BMI, and waist circumference.
- Conduct physical examination.
- Obtain 12-lead ECG (after subject has been supine for at least 5 minutes).
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Obtain an MRI assessment (preferably prior to any histologic evaluation unless a historical biopsy is available).
- Obtain a LiverMultiScan™ reading (dosing Groups 3 or 4 only).
- Undergo a liver biopsy procedure to obtain new tissue (dosing Groups 3 or 4 only).
- Record concomitant medications.
- Record AEs.
- Perform LISSA evaluation.
- Obtain 10-hour fasted clinical laboratory samples for the following:
    - Chemistry
    - CBC
    - HbA1c
    - Insulin level
    - HOMA-IR calculation
    - [redacted]
    - INR
    - Serum pregnancy test (all female subjects)
    - Lipid panel
    - Lipoprotein particles
    - [redacted]
    - Lipase
    - C4 and serum bile acids
    - Vitamin D
    - [redacted]
    - Cytokines
    - PK (pre-dose)
    - ADAs
    - NAbs
    - Exploratory biomarker #1

- Exploratory biomarker #2
- ELF panel
- [redacted]
- [redacted]

- Obtain stool sample for microbiome and fecal fat assessment.
- Obtain urine sample for UA.

In-clinic dosing:
- Collect old NGM282 study-drug kit/diary and conduct reconciliation.
- Collect old rosuvastatin bottle and conduct reconciliation.
- Dispense new rosuvastatin ***(only for subjects who were on statin therapy at Baseline)***.
- Oversee subject's NGM282 study-drug self-administration (from old kit) (not applicable for Early Withdrawal subjects).

Before clinic discharge (and approximately 20 minutes after dosing):
- Obtain 2-hour post-dose PK blood sample.
- Record AEs.
- Perform LISSA evaluation.
- Schedule subject for Week 18 (End of Study) Visit.

(NOTE: Before-clinic-discharge assessments [PK sampling, AE recording, and LISSA evaluation] are not applicable for Early Withdrawal subjects. However, Early Withdrawal subjects should be scheduled for a 6-week Follow-up Visit.)

9.4.8 Week 18 (End of Study) Procedures

This visit will be performed 6 weeks after the last dose of study medication. Subjects will report to this visit fasted. The following procedures will be performed at the Week 18 visit:

- Measure body weight, BMI, and waist circumference.
- Conduct physical examination.
- Obtain 12-lead ECG (after subject has been supine for at least 5 minutes).
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Obtain an MRI assessment (preferably prior to any histologic evaluation unless a historical biopsy is available).
- Obtain a LiverMultiScan^{TM} reading (dosing Groups 3 or 4 only).
- Record concomitant medications.
- Record AEs.

- Obtain 10-hour fasted clinical laboratory samples for the following:
  - Chemistry
  - CBC
  - HbA1c
  - Insulin level
  - HOMA-IR calculation
  - [redacted]
  - INR
  - Serum pregnancy test (all female subjects)
  - Lipid panel
  - Lipoprotein particles
  - [redacted]
  - Lipase
  - C4 and serum bile acids
  - Vitamin D
  - [redacted]
  - Cytokines
  - PK (pre-dose)
  - ADAs
  - NAbs
  - Exploratory biomarker #1
  - Exploratory biomarker #2
  - ELF panel
  - [redacted]
  - [redacted]
- Obtain urine sample for UA.
- Perform pre-dose LISSA evaluation only.
- Collect old rosuvastatin bottle and conduct reconciliation ***(only for subjects who were on statin therapy at Baseline)***.

9.5 Schedule of Study Procedures for Placebo-controlled 24-Week Histology Cohort

The Schedule of Study Procedures for the placebo-controlled 24-week histology cohort is shown in Table 4. The visits should occur as close to the intended dates as possible. However, there is an acceptable ± 3-day window for individual scheduled visits unless stipulated otherwise for specific procedures.

The screening window may be extended an additional 2 weeks (for a total window of 42 days) if additional time is needed to complete procedures. Medical Monitor/designee approval will be required and will not be considered a protocol deviation:

Subjects attending any visits out of windows from Day 1 to Week 24/Early Withdrawal (EOT) visit should be brought back into compliance with the overall study-visit schedule as soon as possible thereafter. Subjects will then return to the clinic at Week 30 (or 6 weeks after last dose) for an EOS follow-up visit.

The Investigator has discretion to repeat assessments if he/she believes the results do not accurately represent the patient's true values. Repeat assessments must be conducted within the Screening Period.

Table 4. Schedule of Study Procedures for Placebo-Controlled 24-Week Histology Cohort

Study Procedure	D –28 to –1 (Screening) [a]	D 1	W 2	W 4	W 6	W 8	W 12	W 18	W 24/ EW (EOT)	W 30 (EOS)
Visit Window (Days)	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3
Informed consent	X									
Demographics	X									
Medical history	X									
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X	X								
Height	X									
Body weight, BMI, waist circumference	X	X					X		X	X
Physical exam	X	X		X		X	X	X	X	X
12-lead ECG	X	X					X		X	X
Vital signs	X	X	X	X	X	X	X	X	X	X
Adverse events (AEs) [k]	X	X	X	X	X	X	X	X	X	X
Chemistry [fasted ≥ 10 hrs]	X	X [je]	X [e]	X [e]	X [e]	X [e]	X [e]	X [e]	X [e]	X [e]
Complete blood count (CBC)	X	X	X	X	X	X	X	X	X	X
HbA1c	X	X					X		X	X
Insulin level and HOMA-IR	X	X					X		X	X
[redacted]		[redacted]					[redacted]		[redacted]	[redacted]
International Normalized Ratio (INR)	X	X					X		X	X
Alpha fetoprotein (AFP)	X									
Pregnancy test [f]	X	X							X	X
Hepatitis and HIV screen	X									
Urinalysis (UA)	X	X					X		X	X
Urine drug screen	X									
Fasting lipid panel	X	X [e]	X [e]	X [e]	X [e]	X [e]	X [e]	X [e]	X [e]	X [e]
Lipoprotein particles		X		X		X	X		X	X
Lipase		X		X		X	X		X	X
C4 and serum bile acids		X	X	X	X	X	X	X	X	X
Vitamin D		X					X		X	X
PK blood samples [g]		X	X	X	X	X	X	X	X	X
Anti-drug antibodies (ADAs)		X	X	X	X	X	X	X	X	X
Neutralizing antibodies (NAbs)		X	X	X	X	X	X	X	X	X
ELF Panel		X			X		X		X	X
Exploratory plasma biomarkers 1, 2		X	X	X	X	X	X	X	X	X

Table 4. Schedule of Study Procedures for Placebo-Controlled 24-Week Histology Cohort (cont'd)

Study Procedure	D –28 to –1 (Screening) [a]	D 1	W 2	W 4	W 6	W 8	W 12	W 18	W 24/ EW (EOT)	W 30 (EOS)
Visit Window (Days)	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3
Exploratory serum biomarker 3		X	X	X	X	X	X	X	X	X
MRI [b]	X				X		X		X	X
[redacted]	[redacted]								[redacted]	
[redacted]	[redacted]								[redacted]	
Liver biopsy [d]	X								X	
IWRS screening registration	X									
IWRS randomization		X								
LISSA evaluations		X	X	X	X	X	X	X	X	X
NGM282 in-clinic self-administration		X	X	X	X	X	X	X	X	
Dispense NGM282 [1]		X	X	X	X	X	X	X		
Dispense rosuvastatin [h]			X	X		X	X	X	X	
Medication compliance			X	X	X	X	X	X	X	X [i]
Lipid-Lowering Therapy Assessment			X	X		X	X			

ADA = anti-drug antibody; AE = adverse event; AFP = alpha fetoprotein; BMI = body mass index; C4 = 7-alpha-hydroxy-4-cholesten-3-one; CBC = complete blood count; D = Day; ECG = electrocardiogram; ELF = enhanced liver fibrosis; EOS = End of Study; EOT = End of Treatment; EW = Early Withdrawal; HIV = human immunodeficiency virus; HOMA-IR = homeostasis model assessment–estimated insulin resistance; hr. = hour; [redacted]; INR = International Normalized Ratio; IWRS = Interactive Web Response System; LISSA = local injection-site symptom assessment; [redacted];
MRI = magnetic resonance imaging;
NAb = neutralizing antibody; PK = pharmacokinetic; UA = urinalysis; W = week.

[a] There should be a minimum of 14 days between Screening and Day 1 visits for adequate separation of the repeated Chemistry (liver function tests) and International Normalized Ratio assessments. Screening window may be extended an additional 2 weeks (total window of 42 days). Medical monitor approval will be required and will not be considered a deviation.

[b] Screening MRI will serve as baseline for efficacy endpoint analysis. Adiposity assessments will be collected as part of the standard MRI procedure at all sites. MRI may be used for up to 8 weeks from the date of the original scan, including use for re-screened subjects

[c] [redacted]

[d] A liver biopsy result is required at Screening and at Week 24. A historical biopsy within 3 months of Screening may be used instead of undergoing a new procedure. Week 24 biopsy should be obtained before the last dose of NGM282 or placebo with a visit window of -7 days and +3 days

[e] Lab results for ALT, AST, Total Cholesterol, LDL, HDL and triglycerides are blinded to site from Week 2 onward. Patient reports to clinic fasted on Day 1 or is rescheduled. All other clinic visits, chemistries and lipid panel will need to be retested if not fasted.

[f] A serum pregnancy test will be performed on all female subjects of child bearing potential at Screening, Week 24, and Week 30. A urine pregnancy test will be performed on all female subjects of child bearing potential at Day 1 (pre-dose).

[g] PK blood samples will be collected in all subjects before dosing themselves in the clinic (pre-dose) and at 2 hours (±20 mins) post-dose at Day 1, Week 12, and Week 24.

[h] Rosuvastatin will be dispensed at Weeks 2, 4, 8, 12 and 18 visits and subjects will be provided further dosing instruction based on their LDL-C levels and whether they are statin-naïve versus statin experienced. Subjects on a statin at screening will be dispensed additional rosuvastatin at Week 24 and continue through Week 30.

[i] Compliance with Rosuvastatin will be assessed at Week 30 for statin-experienced subjects only
[j] Baseline ALT reported result calculated using the median of the Screening and Day 1 value
[k] Adverse events will be monitored and recorded from patient signing informed consent through follow-up.
[l] Subjects will be instructed to self-inject NGM282 or placebo as close to the same time as possible each day in the abdomen and administer the next dose the following morning. Subjects will not self-inject NGM282 at home on clinic visit days.

9.6 Study Visit Procedures for Placebo-controlled 24-week Histology Cohort

9.6.1 Day –28 to Day –1 (Screening) Procedures

Subjects will report to clinic fasted. The following screening procedures should be performed within 28 days prior to dosing. The screening window may be extended an additional 2 weeks (for a total window of 42 days) if additional time is needed to complete procedures. Medical Monitor/designee approval will be required and will not be considered a protocol deviation:

- Obtain informed consent.
- Collect demographic data.
- Ascertain medical history.
- Record prior and concomitant medications.
- Assess inclusion/exclusion criteria.
- Measure height.
- Measure body weight, BMI, and waist circumference.
- Conduct physical examination.
- Obtain 12-lead ECG (after subject has been supine for at least 5 minutes).
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Obtain blood and urine for 10-hour fasted laboratory sample collection
- Obtain an MRI assessment (preferably prior to any histologic evaluation unless a historical biopsy is available). Re-screen subjects may use previously obtained MRI if within 8 weeks from original procedure.
- [redacted]
- Obtain viable tissue slides from historical liver biopsy (within 3 months of screening) or undergo a liver biopsy procedure to obtain new tissue.
- Record AEs (starting from the when the patient signs informed consent)
- Register screened subject in IWRS

9.6.2 Day 1 Procedures

Subjects will report to clinic fasted or be rescheduled. The Day 1 visit should be a minimum of 14 days from the Screening visit in order to allow for adequate separation of repeated

chemistry (liver function tests) and INR laboratory assessments as necessary. The following procedures will be performed at the Day 1 Visit:

Pre-dose:

- Reassess inclusion/exclusion criteria.
- Measure body weight, BMI, and waist circumference.
- Conduct physical examination.
- Obtain 12-lead ECG (after subject has been supine for at least 5 minutes).
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Record concomitant medications.
- Record new and/or changes to AEs.
- Obtain blood and urine for 10-hour fasted laboratory samples
  - Reminder to perform urine pregnancy test for females of child bearing potential

In-clinic dosing and assessments:

- Reconfirm eligibility and no change in clinical symptoms or other evidence of a significant change in liver function from Screening.
- Confirm no new or changes to medications
- Randomize subject in IWRS for NGM282 study drug kit assignment.
- Dispense initial NGM282 study drug kits (2) and home diary
- Provide NGM282 study drug self-administration training.
- Oversee subject's NGM282 study drug self-administration.
- Perform LISSA evaluation.

Before clinic discharge:

- Obtain 2-hour post-dose PK sample.
- Remind subject to bring study drug kits/diary and to not self-inject NGM282 at home on clinic visit days
- Schedule Week 2 visit and remind subject for home dosing to administer NGM282 or placebo as close as possible to the same time each day

9.6.3 Week 2 Procedures

Subjects will report to clinic fasted and not dosed with NGM282. The following procedures will be performed:

Pre-dose:

- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).

- Obtain blood for 10-hour fasted clinical laboratory samples (if not fasted, chemistries and lipid panel will need to be retested)
  - Results are blinded for ALT, AST, Total Cholesterol, LDL, HDL and triglycerides
- Record concomitant medications.
- Record new and/or changes to AEs.

In-clinic dosing and dispensing:

- Collect old NGM282 study-drug kit/diary and conduct reconciliation.
- Dispense new NGM282 study-drug kits (2) and diary.
- Dispense rosuvastatin medication/diary
- Oversee subject's NGM282 study-drug self-administration (from new kit).
- Perform LISSA evaluation.

Before clinic discharge:

- Remind subject to bring study drug kits/diary and to not self-inject NGM282 at home on clinic visit days.
- Schedule Week 4 visit and remind subject for home dosing to administer NGM282 or placebo as close as possible to the same time each day

Lipid-Lowering Therapy Assessment:

- NGM Medical Monitor/designee will evaluate LDL-C level as outlined in Section 10.4 and inform site to:
  - Start or not start rosuvastatin therapy
  - Continue with current therapy
  - Switch to rosuvastatin therapy
- The site will then contact the subject with further instructions

9.6.4 Week 4 Procedures

Subjects will report to clinic fasted and not dosed with NGM282. The following procedures will be performed:

Pre-dose:

- Conduct physical examination.
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).

- Obtain blood for 10-hour fasted clinical laboratory samples (if not fasted chemistries and lipid panel will need to be retested)
  - Results are blinded for ALT, AST, Total Cholesterol, LDL, HDL and triglycerides
- Record concomitant medications.
- Record new and/or changes to AEs.

In-clinic dosing and dispensing:

- Collect old NGM282 study-drug kit/diary and conduct reconciliation.
- Collect old rosuvastatin medication bottle/diary and conduct reconciliation.
- Dispense new NGM282 study-drug kits (2) and diary.
- Dispense new rosuvastatin medication/diary.
- Oversee subject's NGM282 study-drug self-administration (from new kit).
- Perform LISSA evaluation.

Before clinic discharge:

- Remind subject to bring study drug kits/diary and to not self-inject NGM282 at home on clinic visit days.
- Schedule Week 6 visit and remind subject for home dosing to administer NGM282 or placebo as close as possible to the same time each day

Lipid-Lowering Therapy Assessment:

- NGM Medical Monitor/designee will evaluate LDL-C level as outlined in Section 10.4 and inform site to:
  - Start or not start rosuvastatin therapy
  - Continue current therapy
  - Titrate rosuvastatin therapy
  - Switch to rosuvastatin therapy
- The site will then contact the subject with further instructions

9.6.5 Week 6 Procedures

Subjects will report to clinic fasted and not dosed with NGM282. The following procedures will be performed:

Pre-dose:

- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).

- Obtain blood for 10-hour fasted clinical laboratory samples (if not fasted, chemistries and lipid panel will need to be retested)
  - Results are blinded for ALT, AST, Total Cholesterol, LDL, HDL and triglycerides
- Obtain an MRI assessment.
- Record concomitant medications.
- Record new and/or changes to AEs.

In-clinic dosing and dispensing:
- Collect old NGM282 study-drug kit/diary and conduct reconciliation.
- Dispense new NGM 282 study-drug kits (2) and diary.
- Oversee subject's NGM282 study-drug self-administration (from new kit).
- Perform LISSA evaluation.

Before clinic discharge:
- Remind subject to bring study drug kits/diary and to not self-inject NGM282 at home on clinic visit days.
- Schedule Week 8 visit and remind subject for home dosing to administer NGM282 or placebo as close as possible to the same time each day

9.6.6 Week 8 Procedures

Subjects will report to clinic fasted and not dosed with NGM282. The following procedures will be performed:

Pre-dose:
- Conduct physical exam.
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Obtain blood for 10-hour fasted clinical laboratory samples (if not fasted, chemistries and lipid panel will need to be retested)
  - Results are blinded for ALT, AST, Total Cholesterol, LDL, HDL and triglycerides
- Record concomitant medications.
- Record new and/or changes to AEs.

In-clinic dosing and dispensing:
- Collect old NGM282 study-drug kit/diary and conduct reconciliation.
- Collect old rosuvastatin medication bottle/diary and conduct reconciliation.
- Dispense new NGM282 study-drug kits (4) and diary.

- Dispense new rosuvastatin medication/diary.
- Oversee subject's NGM282 study-drug self-administration (from new kit).
- Perform LISSA evaluation.

Before clinic discharge:

- Remind subject to bring study drug kits/diary and to not self-inject NGM282 at home on clinic visit days.
- Schedule Week 12 visit and remind subject for home dosing to administer NGM282 or placebo as close as possible to the same time each day

Lipid-Lowering Therapy Assessment:

- NGM Medical Monitor/designee will evaluate LDL-C level as outlined in Section 10.4 and inform site to:
  - Continue with current therapy
  - Titrate rosuvastatin therapy
- The site will then contact the subject with further instructions

9.6.7 Week 12 Procedures

Subjects will report to clinic visit fasted and not dosed with NGM282. The following procedures will be performed:

Pre-dose:

- Measure body weight, BMI, and waist circumference.
- Conduct physical examination.
- Obtain 12-lead ECG (after subject has been supine for at least 5 minutes).
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Obtain blood and urine for 10-hour fasted clinical laboratory samples (if not fasted, chemistries and lipid panel will need to be retested)
  - Results are blinded for ALT, AST, Total Cholesterol, LDL, HDL and triglycerides
- Obtain an MRI assessment.
- Record concomitant medications.
- Record new and/or changes to AEs.

In-clinic dosing and dispensing:

- Collect old NGM282 study-drug kit/diary and conduct reconciliation.
- Collect old rosuvastatin medication bottle/diary and conduct reconciliation.

- Dispense new NGM282 study-drug kits (5) and diary.
- Dispense new rosuvastatin medication/diary.
- Oversee subject's NGM282 study-drug self-administration (from new kit).
- Perform LISSA evaluation.

Before clinic discharge:

- Obtain 2-hour post-dose PK blood sample.
- Remind subject to bring study drug kits/diary and to not self-inject NGM282 at home on clinic visit days.
- Schedule Week 18 visit and remind subject for home dosing to administer NGM282 or placebo as close as possible to the same time each day

Lipid-Lowering Therapy Assessment:

- NGM Medical Monitor/designee will evaluate LDL-C level as outlined in Section 10.4 and inform site to:
  - Continue with current therapy
  - Evaluate additional lipid-lowering therapy with ezetimibe for statin non-responder
  - For subjects taking statins, evaluate tolerability and if deemed necessary, subject may be considered for alternative second-line lipid lowering therapy with ezetimibe .
- The site will then contact the subject with further instructions

9.6.8 Week 18 Procedures

Subjects will report to clinic fasted and not dosed with NGM282. The following procedures will be performed:

Pre-dose:

- Conduct physical examination.
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Record concomitant medications.
- Record new and/or changes to AEs.
- Obtain blood for 10-hour fasted clinical laboratory samples (if not fasted chemistries and lipid panel will need to be retested)
  - Results are blinded for ALT, AST, Total Cholesterol, LDL, HDL and triglycerides

In-clinic dosing and dispensing:

- Collect old NGM282 study-drug kit/diary and conduct reconciliation.
- Collect old rosuvastatin medication bottle/diary and conduct reconciliation.
- If subject is taking statins, evaluate tolerability and continue therapy to Week 24 for statin naïve or Week 30 for statin experienced
- Dispense new NGM282 study-drug kits (5) and diary.
- Dispense new rosuvastatin medication/diary.
- Oversee subject's NGM282 study-drug self-administration (from new kit).
- Perform LISSA evaluation.

Before clinic discharge:

- Remind subject to bring study drug kits/diary and to not self-inject NGM282 at home on clinic visit days.
- Schedule Week 24 (End of Treatment) visit and remind subject for home dosing to administer NGM282 or placebo as close as possible to the same time each day

9.6.9 Week 24/Early Withdrawal (End of Treatment) Procedures

Subjects will report to clinic fasted and not dosed with NGM282. The following procedures will be performed:

Pre-dose:

- Measure body weight, BMI, and waist circumference.
- Conduct physical examination.
- Obtain 12-lead ECG (after subject has been supine for at least 5 minutes).
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).

- Obtain blood and urine for 10-hour fasted clinical laboratory samples (if not fasted, chemistries and lipid panel will need to be retested)
  - Results are blinded for ALT, AST, Total Cholesterol, LDL, HDL and triglycerides
- Obtain an MRI assessment
  - MRI should be obtained before the last dose of NGM282 (standard Table 4 visit window applies)
- [redacted]
- Undergo a liver biopsy procedure to obtain new tissue
  - Results will be blinded.
  - Biopsy should be obtained before the last dose of NGM282 with a visit window of -7 days and +3 days

- Record concomitant medications.
- Record new and/or changes to AEs.

In-clinic dosing and dispensing:

- Collect old NGM282 study-drug kit/diary and conduct reconciliation.
- Collect old rosuvastatin medication bottle/diary and conduct reconciliation.
- If stain experienced subject is taking statins, evaluate tolerability and continue therapy to Week 30
- Statin naïve subjects taking statins are to discontinue therapy
- Dispense new rosuvastatin medication/diary to statin experienced subjects taking therapy
- Oversee subject's NGM282 study-drug self-administration (from old kit) (not applicable for Early Withdrawal subjects).
- Perform LISSA evaluation.

Before clinic discharge:

- Obtain 2-hour post-dose PK blood sample (except early withdrawal subjects).
- Schedule Week 30 (End of Study) Visit.

9.6.10 Week 30 (End of Study) Procedures

This visit will be performed 6 weeks after the last dose of study medication. Subject will report to clinic fasted. The following procedures will be performed:

- Measure body weight, BMI, and waist circumference.
- Conduct physical examination.
- Obtain 12-lead ECG (after subject has been supine for at least 5 minutes).
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse).
- Obtain blood and urine for 10-hour fasted clinical laboratory samples
  - Results are blinded for ALT, AST, Total Cholesterol, LDL, HDL and triglycerides
- Obtain an MRI assessment
- Record concomitant medications.
- Record new and/or changes to AEs.
- Perform LISSA evaluation.
- Collect old rosuvastatin medication bottle/diary and conduct reconciliation for statin experienced subjects taking therapy

9.7 Prior and Concomitant Medications

Concomitant therapies are any prescription or over-the-counter preparations used by a subject while participating in this study and must be recorded from 28 days prior to Day 1 until end of study.

Subjects should refrain from the use of any new medications or products or change in the dose or frequency of existing therapies during Screening and throughout the study. The Medical Monitor should be informed of any changes or addition of medications during this time period.

Prohibited Medications from 28 days prior to Day 1 and throughout study:

- Investigational agents, other than NGM282, or devices for any indication
- Known hepatotoxic agents
- Agents used for the treatment of any condition listed in the exclusionary enrollment criteria (see Section 8.1.2)
- Any hepatotoxic herbal medications other than standard vitamin supplements

Placebo-Controlled 24 Week Histology Cohort Only:

- Investigational agents, other than NGM282, or devices for any indication
- Agents used for the treatment of any condition listed in the exclusionary enrollment criteria (see Section 8.1.2)
- Hepatotoxic agents outlined in (Appendix E).
    - All other hepatotoxic agents will be left to the discretion of the PI. There should be clear documentation in the patient study records of PI approval of use.

Prohibited Medications within 3 months of Screening and throughout study:

- Ezetimibe, colesevelam, cholestyramine, niacin, PCSK9 inhibitors, or other lipid-lowering agents (except Double-blind)

Placebo-Controlled 24 Week Histology Cohort Only:

- Contraindicated medications according to rosuvastatin package insert (Appendix C)
    - Includes cyclosporine, gemfibrozil, protease inhibitors (atazanavir, ritonavir, lopinavir, simeprevir), coumarin anticoagulants, fenofibrates, niacin and colchicine
- Contraindicated medications according to ezetimibe package insert (Appendix D)
    - Includes cyclosporine, fenofibrate, cholestyramine and coumarin anticoagulants

- Use of any other lipid lowering agents or combination preparation of statins, within 3 months of Screening and throughout study, **except** ezetimibe when approved by MM/designee as second line lipid management therapy.
    - colesevelam, cholestyramine, niacin, PCSK9 inhibitors (evolocumab or alirocumab), colestid, fibrates, fenofibrates, pharmacologic/prescribed fish oil
    - Use of weight loss medications including: orlistat, phentermine, topiramate, qsymia, lorcaserin hydrochloride, naltrexone hydrochloride, liraglutide (for weight loss not T2D, e.g. Saxenda), benzphentamine, diethylpropion and phendimetrazine

Acceptable Medications that require a stable regimen prior to and throughout study**:**

Double-Blind and Single-Blind, Open-Label Cohorts:

- Diabetes medications (except GLP1 agonists): requires a stable regimen for at least 3 months prior to Day 1.
- GLP1 agonists: requires a stable regimen 12 months prior to Day 1.
- Weight-loss medications: requires stable regimen for at least 3 months prior to Day 1 with no safety or tolerability events.
- Other therapies for NAFLD or NASH: requires a stable regimen for at least 6 months prior to Screening biopsy and throughout the study. May include vitamin E, milk thistle, thiazolidinediones and pentoxifylline.

Placebo-Controlled 24 Week Histology Cohort Only:

- GLP1 agonists and pioglitazone: requires a stable regimen 12 months prior to Day1.
- Procedural Medications use (e.g. Anti-anxiety medication for MRI scan, anesthetic for liver biopsy) will be at the discretion of the PI and documented accordingly.
- Other therapies for NAFLD or NASH: requires a stable regimen for at least 3 months prior to Screening biopsy and throughout the study. May include vitamin E (>800 IU), milk thistle, and pentoxifylline.

Statin Use:

Double-Blind Cohort:

Includes statins.

Open-Label Single-Blind and Placebo-Controlled 24 Week Histology Cohorts:

Includes statins if the following conditions are met:

1. Subject can be defined as statin naïve or experienced at Screening based on the following definitions:
   a. **Statin-naïve**: no administration of statins within 3 months prior to enrollment.
   b. **Statin experienced**: administration of ≤ 50% of the maximal dose of current statin therapy.
2. Requires a stable regimen for at least 3 months prior to Screening through Week 2.

The following are the acceptable daily doses of currently approved statin therapies, including combination preparations of statins and other lipid-lowering agents.

- Atorvastatin: ≤ 40 mg/d
- Fluvastatin: ≤ 40 mg/d
- Lovastatin: ≤ 40 mg/d (immediate release), ≤ 30 mg/d (extended release)
- Pitavastatin: ≤ 2 mg/d
- Pravastatin: ≤ 40 mg/d
- Rosuvastatin: < 20 mg/d (Note: must be < not ≤ 20 mg/d)
- Simvastatin: ≤ 40 mg/d

9.8 Diet and Activity Control

Subjects should maintain their normal level of physical activity, diet, and lifestyle throughout the entire study (i.e., will not begin a new exercise program or participate in any unusually strenuous physical exertion).

9.9 Clinical Evaluations

9.9.1 Liver Biopsy

Subjects who meet the Screening criteria of an available liver biopsy tissue specimen within 6 months of Screening for the double-blind cohort and 12 months for the single-blind open-label cohort will not be required to undergo a liver biopsy. For the dosing Groups 3 or 4 of the open-label single-blind cohort and for the placebo-controlled 24-week histology cohort, the liver biopsy must be performed within 3 months of Screening in order to serve as the Baseline comparison for the additional Week 12 biopsy. All other subjects will be required to undergo a liver biopsy per the study site's local standard-of-care procedure during the Screening period and prior to randomization. Tissue from all subjects will be prepped and read by a qualified pathologist for review for the absence/presence of NASH. Liver biopsies

with histologically confirmed NASH will be further assessed by a qualified pathologist using the NAS and Fibrosis Score established and validated by the NASH Clinical Research Network (see Appendix A). Liver biopsies will be assessed for degree of steatosis (0–3), lobular inflammation (0–3), hepatocellular ballooning (0–2), and fibrosis (0-4). The first three components will be added together to determine the NAS that ranges from 0 to 8. Liver biopsies with a NAS of < 4 will be considered exclusionary. Subjects with liver biopsies with Stage 0 (no fibrosis) or Stage 4 fibrosis (cirrhosis) will be excluded from this study. For the placebo-controlled 24-week histology cohort, only subjects with Stage 2 or Stage 3 fibrosis will be allowed to enroll into the study.

The Screening and EOT biopsies for dosing Groups 3 or 4 of the open-label single-blind cohort and all subjects in the placebo-controlled 24-week histology cohort will be read by a single central pathologist. The biopsies will be read and scored using the same NASH Clinical Research Network (CRN) scores as the inclusion biopsies. These will be read unpaired and blinded to subject and reported separately from the inclusion biopsy.

For the placebo-controlled 24-week histology, only the Week 24 biopsy results will be blinded to the site and subject. Screening biopsy results will not be blinded. The Week 24 biopsy should be obtained before the last dose of NGM282 with a visit window of -7 days and +3 days.

9.9.2 Magnetic Resonance Imaging (MRI)

All enrolled subjects will have a Baseline (from the Screening result) and EOT MRI of the liver to evaluate liver volume and liver fat. Open-label single-blind cohort subjects are requested to undergo an additional MRI at Weeks 6 and 18.

Subjects in the placebo controlled 24–week histology cohort will have an MRI performed at Screening and at Weeks 6, 12, 24, and 30. None of the treatment or post treatment MRI results (other than incidental findings) will be provided to the sites. MRI-PDFF should be performed before the last dose of NGM282

MRI-PDFF will be reported on all MRI imaging scans. Scans should be performed at high field strength (3T preferred, 1.5T acceptable), without the administration of oral or intravenous contrast material. MRI examinations will include a six-echo gradient recalled echo (GRE) sequence (2D preferred, 3D acceptable), [redacted]

The initial study MRI examination will be performed during the Screening period prior to randomization. An MRI-PDFF value of ≥ 8% at Screening as assessed by the central radiology core is one of the inclusion criteria for the study. Therefore, for patients who require a liver biopsy as part of the trial (for whom no recent liver biopsy is available), it is

recommended that liver biopsy be scheduled no sooner than 7 business days after (electronic) transmission of the screening MRI examination to the central radiology core to allow adequate time for processing and reporting of the result. MRI-PDFF results will be reported to the individual site no more than 5 business days after the MRI examination is received.

For both Screening and EOT/Early Withdrawal MRI examinations, subjects should consume nothing by mouth (NPO) for 4 hours prior to their MRI appointment. Medications and small amounts of water are acceptable.

Prior to MRI, all subjects should undergo safety assessment per institutional protocols and per the guidelines of the local Institutional Review Board. Subjects should be questioned regarding claustrophobia, pregnancy or potential pregnancy, size or weight exceeding the capabilities of the MRI system, metal implants, and other potential safety issues.

Detailed instructions for MRI procedures and provision of examination to a central reader will be presented in a separate MRI Manual.

LiverMultiScan™ imaging will be also be collected during the MRI to obtain the MRI-PDFF assessments in dosing Groups 3 or 4 of the open-label single-blind cohort and all subjects in the placebo-controlled 24-week histology cohort. This scan is optional and will only be performed where the imaging technology is available and adequate. The subjects will be required to stay in the MRI machine approximately 10 minutes longer than the standard MRI procedure. The software uses the images of the liver to calculate parameters that have been shown to correlate with histological measures of steatosis, hepatic iron overload, and fibrosis of the liver (Banerjee 2014). Additionally, an LIF score and corrected cT1 value are also calculated, both of which have been correlated to liver histology as well as predicting liver-related outcomes (Banerjee 2014, Pavlides 2016, Perspectum Diagnostics, data on file).

Detailed instructions for the LiverMultiScan™ software and provision of the imaging to a central reader will be presented in a separate manual.

[redacted]. There are no current imaging techniques that can directly detect the specific stage of fibrosis. Most attempt to detect fibrosis indirectly using proposed biomarkers which include: stiffness, diffusion, perfusion, metabolites, and image texture with the leading biomarker being liver stiffness (Younossi 2017). [redacted]

9.9.3 Pharmacokinetic Blood Sample Collection and Processing

In all cohorts, blood samples for PK analysis of NGM282 levels will be collected before dosing on all study visits. On Day 1 and Week 12, an additional PK blood sample will be collected 2 hours post-dose (±20 mins). Additionally, in the open-label single-blind cohort, up to 8 subjects per dosing group in the single-blind open-label cohort will be given the option to participate in further PK sampling at pre-dose (Baseline) and at 1, 2, 4, 8, and 12 hours (±20 mins) after dosing on Day 1 (Baseline) and Week 6. Subjects participating in the PK sub-study will not obtain an additional 2-hour post-dose sample.

Processing, storage, and shipping instructions for these PK blood samples will be presented in the study Lab Manual.

9.9.4 Clinical Laboratory Evaluations

Clinical laboratory evaluations including chemistry (fasted at least 10 hours), CBC, and UA will be collected as outlined in the respective Schedules of Study Procedures (double-blind, Table 2; open-label, Table 3; placebo-controlled 24-week histology, Table 4).

Laboratory assessments of fasted lipid panel (total cholesterol, LDL, HDL, and TG), lipoprotein particles, HbA1c, insulin, HOMA-IR, and FFAs will be performed as outlined in the respective Schedules of Study Procedures (double-blind, Table 2; open-label, Table 3; placebo-controlled 24-week histology, Table 4). For the placebo-controlled 24 week histology, test results will be monitored by the sponsor's medical monitor/designee, but are blinded to the site and subject for ALT, AST, Total Cholesterol, LDL, HDL and triglycerides for Week 2 – Week 30 sample collections. LDL-direct may be used if LDL-C was not able to be analyzed.

Laboratory assessments for C4 and serum bile acids will be performed as outlined in the respective Schedules of Study Procedures (double-blind, Table 2; open-label, Table 3; placebo-controlled 24-week histology, Table 4).

Laboratory assessments for changes in bile-mediated absorption as measured by vitamin D and INR will be performed as outlined in the respective Schedules of Study Procedures (double-blind, Table 2; open-label, Table 3; placebo-controlled 24-week histology, Table 4).

[redacted]

Cytokines (IL-6, and TGF-β) and hs-CRP will be assessed as outlined in the respective Schedules of Study Procedures (double-blind, Table 2; open-label, Table 3).

Hepatitis screen and HIV antibody screen will be performed at Screening.

A urine screen for drugs of abuse will be performed at Screening.

A stool sample will be collected at Day 1 and Week 12 in only the double-blind and open-label single-blind cohorts. Stool samples will be analyzed for microbiome (bacterial composition) and fecal fat content (double-blind, Table 2; open-label, Table 3).

A serum qualitative pregnancy test (all female patients of child bearing potential) will be performed at Screening and Week 24/EOT and Week 30/EOS. A urine pregnancy test (all female patients of child bearing potential) will be performed at Day 1 (pre-dose).

AFP will be measured at Screening.

Samples for analysis of ADAs, NAbs, and exploratory biomarkers will be collected as outlined in the respective Schedules of Study Procedures (double-blind, Table 2; open-label, Table 3; placebo-controlled 24-week histology, Table 4). All NAb samples will be collected as scheduled, and analyzed only if necessary based on ADA results.

Exploratory biomarkers, ELF panel, [redacted] will be assessed as outlined in the respective Schedules of Study Procedures (open-label, Table 3; placebo-controlled 24-week histology, Table 4).

Processing, storage, and shipping instructions for the above will be presented in a separate Lab Manual.

9.9.5 12-Lead Electrocardiograms

12-lead ECGs will be performed after the subject has been supine for at least 5 minutes, and as outlined in the respective Schedules of Study (double-blind, Table 2; open-label, Table 3; placebo-controlled 24-week histology, Table 4).

9.9.6 Vital Signs

Vital signs (including temperature, respiratory rate, and seated blood pressure and pulse) will be obtained at Screening and at all study visits as outlined in the respective Schedules of Study Procedures (double-blind, Table 2; open-label, Table 3; placebo-controlled 24-week histology, Table 4).

Seated blood pressure and pulse will be measured after the subject has been seated for at least 5 minutes.

9.9.7 Physical Examinations

A routine physical examination will be performed at selected study visits in each of the cohorts as outlined in the Schedule of Study Procedures (double-blind, Table 2; open-label, Table 3; placebo-controlled 24-week histology, Table 4.

9.9.8 Weight, Body Mass Index, and Waist Circumference Measurements

Subjects will be weighed, BMI calculated, and waist circumference measured at Screening, and selected study visits as outlined in the Schedule of Study Procedures (double-blind, Table 2; open-label, Table 3; placebo-controlled 24-week histology, Table 4). Formal instructions for recording weight and measuring waist circumference will be provided to sites.

9.9.9 Local Injection-Site Symptom Assessments (LISSA)

Injection-site evaluation will be made and documented (including photographs, as needed) by the PI or clinic staff using a LISSA (Appendix B).

The LISSA is to be administered pre- and post-dose (approximately 20 minutes after injection) at Day 1 through EOT in the double-blind and open-label single-blind cohorts. A single assessment will be performed at the Week 16 (double-blind cohort) or Week 18 (open-label single-blind cohort), to assess any prior dose injection site reactions.

For the placebo-controlled 24-week histology cohort, LISSA evaluations are to be performed at each clinic visit from Day 1 through Week 30.

The instructions below are to be followed for the pre-dose LISSA:

- The injection site area(s) should be examined for any ISRs at every visit.
- If a single ISR is observed, the LISSA should be used to rate that ISR.
- If multiple ISRs are observed, the LISSA should be used to rate the most severe ISR.
- The study visit note should document the total number of ISRs seen on examination.

The LISSA is intended to be a “snapshot” of the ISRs at the time of clinic assessment. The LISSA is not intended to capture ISR data (frequency, severity, duration, etc.) in between clinic visits. As with any other potential AE, Investigator judgment should be used as to whether any ISR is recorded as an AE. Mild to Severe Reactions (LISSA Grades 1–3) are reported as AEs at the discretion of the investigator unless standard SAE criteria are met and then must be reported as an SAE. Life-threatening (LISSA Grade 4) meet SAE criteria and must be reported as such.

LISSAs may be performed if necessary and as clinically indicated by the PI to capture ISRs outside of the routine scheduled assessment time points.

The 2007 FDA Toxicity Grading Scale (Appendix B) will be used to assess any ISRs (U.S. Department of Health and Human Services 2007). The documented record will include all of the symptoms, severity, and any local reaction (including pain, tenderness, redness, and swelling) and size of injection-site skin reactions identified and observed by the subject or clinic personnel. LISSA scores will be documented on the subject’s CRF.

10 Study Drug

10.1 Clinical Supplies

10.1.1 NGM282

NGM282 is formulated in aqueous isosmotic buffer solution with 0.01% polysorbate-20. It is filled into 1-mL, type I glass syringes, with a 29-g staked needle, needle shield, grey rubber plunger, and plastic plunger rod. Filled syringes are labeled and packaged into trays and cardboard cartons.

In the double-blind cohort, NGM282 is provided as a sterile solution for injection in a single-use, pre-filled syringe for SC administration at doses of 3 and 6 mg, and volume-matched placebo. In the single-blind cohort, NGM282 is provided as a sterile solution for injection in a single-use, pre-filled syringe for SC administration at doses of 0.3, 1, and 3 mg. In the placebo-controlled 24-Week histology cohort NGM282 is provided as a sterile solution for injection in a single-use, pre-filled syringe for SC administration at 1 mg dose and volume-matched placebo.

The drug product is manufactured for NGM under current Good Manufacturing Practice regulations [redacted] that has undergone FDA inspection.

10.1.2 Rosuvastatin

10.1.2.1 Drug Supply for Open-Label Single-Blind Cohort

For the open-label single-blind cohort, rosuvastatin will be supplied as 20-mg pink, round, convex-shaped, coated tablets with “RU20” on one side and blank on the other side in bottles of 30 tablets (NDC 16252-617-30). The active ingredient is rosuvastatin calcium and inactive ingredients include microcrystalline cellulose, lactose monohydrate, sodium carbonate monohydrate, sodium lauryl sulfate, crospovidone, magnesium stearate, titanium dioxide, polyethylene glycol, polyvinyl alcohol, talc, ferric oxide yellow, ferric oxide red, FD&C Red 40, and indigotindisulfonate sodium.

10.1.2.2 Drug Supply for Placebo-Controlled 24-Week Histology Cohort

For the placebo-controlled 24-week histology cohort, rosuvastatin will be supplied. Rosuvastatin calcium tablets 20 mg are light pink colored, round, biconvex, film coated tablets debossed with '1181' on one side and plain on other side in bottles of 90 tablets (NDC 13668-181-90). The active ingredient is rosuvastatin calcium and inactive ingredients include crospovidone, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, titanium dioxide, triacetin and ferric oxide red.

10.2 Study-Drug Accountability

The PI is responsible for ensuring that a current record of inventory/drug accountability (NGM282 and rosuvastatin) is maintained. Inventory records must be readily available for inspection by the study monitor and are open to inspection by regulatory authorities at any time. Each shipment of drug supply for the study will contain a shipping manifest to assist the PI in maintaining current and accurate inventory records.

Upon receipt of the investigational drug, the designated site personnel will visually inspect the shipment, verify the number and condition of study drug received, and confirm receipt of study drug.

At the completion of the study and after all drug accountability has been performed by the site CRA, all unused study-drug supplies will be returned to the Sponsor (or designee) or disposed of by the clinic, per the Sponsor's (or designee's) written instructions.

10.3 Study-Drug Storage

NGM282 syringes are to be stored at the clinical site in the provided packaging and refrigerated at 2°C–8°C (36°F–46°F) in a secure, controlled-access location protected from light. At the subject's home, NGM282 syringes are to be stored in the provided packaging protected from light and refrigerated. All drug excursions should be reported immediately to Sponsor to confirm NGM 282 stability.

Rosuvastatin calcium tablets should be stored at room temperature, at 68°F–77°F (20°C– 25°C) and in a dry place. Excursions are permitted to 59°F–86°F (15°C– 30°C) Please refer to package insert USP Controlled Room Temperature. (Appendix D)

Subjects will be instructed to take care in keeping both study drugs out of the reach of children and other family members.

10.4 Dose Preparation and Administration

10.4.1 NGM282

Subjects will be instructed to dose with NGM282 at relatively the same time each day. For visit days in the clinic, subjects will not dose at home.

Study-drug syringes should be brought to room temperature (~15-20 minutes) prior to use and administered as a SC injection in the abdomen. On Day 1, subjects will be trained on SC self-injecting. During the on-treatment visits, SC self-injecting will occur in the clinic under observation by clinic staff. Re-training will be provided as required. Written dose preparation and administration instructions will be provided to subjects. Subjects will be required to complete a daily study-drug administration diary.

10.4.2 Rosuvastatin

Only subjects in the open-label single-blind and placebo-controlled 24-week histology cohorts who meet specific on-treatment criteria will be instructed to dose rosuvastatin based on the LDL-C levels at Weeks 2, 4, and 8 or at the discretion of the medical monitor. Additionally, subjects in the placebo-controlled 24-week histology cohort who have not achieved an adequate response or are unable to tolerate statin therapy may be considered for second-line lipid-lowering therapy with ezetimibe at the discretion of the medical monitor.

Ezetimibe is formulated as 10mg tablets and can be administered with or without food at the same time as rosuvastatin. This must be approved by the Sponsor's Medical Monitor prior to dosing with ezetimibe and will be prescribed by the Investigator. The specific treatment algorithms will be based on whether subjects are statin naïve (Section 10.4.2.1) versus statin experienced (Section 10.4.2.2) at Baseline as outlined in the following figures for subjects in both the open-label single-blind and placebo-controlled 24-week histology cohorts:

10.4.2.1 Rosuvastatin Treatment Algorithm – Statin Naïve

10.4.2.2 Rosuvastatin Treatment Algorithm – Statin Experienced

10.5 Removal of Study Blind

Breaking of any blind will be available to the PI through an IWRS. The subject's treatment assignment will be available to the PI in the event of a medical emergency or an AE that necessitated identification of the study drug for the welfare of that subject. Except in the case of a medical emergency, the PI and clinic staff will remain blinded during the conduct of the study and until such time that all discrepancies in the clinical database are resolved (i.e., at the time of the database lock). The date and time when the PI removed the study blind for an individual subject will be documented by the IWRS, and an automated notification will be sent to the Sponsor.

11 Adverse Events

11.1 Definition and Grading Intensity of Adverse Events

An AE is defined as any untoward medical occurrence in a subject of clinical investigational participation administered a pharmaceutical product, whether or not considered drug related. A TEAE is an AE that is reported after a dose of study drug.

AEs include the following:

- Unfavorable changes in general condition
- Subjective or objective signs/symptoms
- Concomitant diseases or accidents
- Clinically relevant adverse changes in laboratory parameters observed in a subject in the course of a clinical study

AEs comprise all disturbances of general health status, subjective and objective disease symptoms (including laboratory abnormalities), and accidents observed in the context of a clinical trial, irrespective of a possible causal relationship with the administration of the trial substance. Events occurring in the framework of a clinical trial during drug-free and post-treatment periods or under placebo are also to be designated as AEs.

All AEs regardless of how identified (e.g., volunteered, elicited, noted on physical examination) will be recorded throughout the study from the time the patient signs informed consent through Follow-up.

Subjects will be followed for resolution of AEs, by querying the subjects for an ongoing AE until resolved or until any unresolved AEs are judged by the PI to have stabilized or if lost to follow-up. Resolution of all AEs will be promptly documented by the clinic on the subject's CRF.

Any pregnancy diagnosed during the study must be reported immediately to the PI and Sponsor, including pregnancy in female partners of male subjects. The pregnancy will be followed to term and/or outcome and this outcome must be reported to the Sponsor. Pregnancy, in and of itself, is not regarded as an AE or SAE unless the birth results in a congenital anomaly/birth defect or there is suspicion that the study medication may have interfered with the effectiveness of a contraceptive medication or method.

The PI will rate the severity of AEs using the CTCAE v4.03 to grade the severity. Each CTCAE v4.03 term is a Medical Dictionary for Regulatory Activities (MedDRA) Lowest Level Term (LLT). The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE. Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection. Grade 5 (Death) is not appropriate for some AEs and, therefore, is not an option.

11.2 Criteria for Determining Relationship to Drug

The PI will make a blinded determination of the relationship of the AE to NGM282 (including placebo) in the double-blind cohort. An open-label determination of the relationship of the AE to NGM282 and a separate open-label determination of the relationship of the AE to rosuvastatin will be made in the open-label single-blind cohort. The PI will make a blinded determination of the relationship of the AE to NGM282 (including placebo) and a separate open-label determination of the relationship of the AE to rosuvastatin in the placebo-controlled 24-week histology cohort. All determinations of relationship will be made using a four-category system (not related, possible, probable, or definite) according to the following guidelines:

- **NOT RELATED** = an AE that does not follow a reasonable temporal sequence from administration of the drug and that can be reasonably explained by other factors, including underlying disease, complications, concomitant drugs, or concurrent treatment;
- **POSSIBLE** = an AE that follows a reasonable temporal sequence from the administration of the drug (including the course after withdrawal of the drug) and that cannot be excluded as being possibly caused by the drug (e.g., existence of similar reports attributed to the drug and/or its analogues; reactions attributable to the pharmacological effect of the drug), although other factors such as underlying disease, complications, concomitant drugs, or concurrent treatment are presumable;
- **PROBABLE** = an AE that follows a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug) and that can be excluded as being possibly caused by other factors, such as underlying disease, complications, concomitant drugs, or concurrent treatment.
- **DEFINITE** = an AE that follows a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug), follows a known or hypothesized cause–effect relationship, and (if appropriate) satisfies the following:
  - Positive results obtained in drug sensitivity tests
  - Toxic level of the drug present in blood or other body fluids

11.3 Reporting

An SAE is any untoward medical occurrence at any dose that results in any of the following outcomes:

- Death
- A life-threatening event (i.e., places the subject, in the view of the PI, at immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

An unexpected adverse drug event is any adverse drug event the specificity or severity of which is not consistent with the current IB or, if an IB is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

An AE is associated with the use of the drug if a reasonable possibility exists that the event may have been caused by the drug.

SAEs that are unexpected and related to either NGM282 or rosuvastatin are reportable to Regulatory Authorities. All SAEs will be reported by the PI to the Sponsor and will be reported to the responsible Ethics Committee (EC) in accordance with local requirements.

The Sponsor's assigned Safety Representative will be notified in writing (e.g., email or facsimile) within 24 hours of when an SAE is first recognized or reported. The Safety Representative will subsequently notify the Sponsor and the Sponsor's assigned Medical Monitor of all reported SAEs.

11.4 Cardiovascular Adjudication

An external independent Cardiovascular Adjudication Committee (CAC) will adjudicate serious adverse events (SAEs). The CAC members will be independent of the Sponsor, the clinical study sites and Investigators. The blinded medical review of known or suspected Major Adverse Cardiovascular Event (MACE) will primarily focus on CV death, myocardial infarction, cerebrovascular accident (stroke), and hospitalization for heart failure. Sites may be asked to provide additional source documentation relevant to any event reported to the CAC as they would to study safety personnel for any serious safety event. Further details are retained in the CAC Charter for the NGM282 Program.

12 Data Analysis and Statistical Considerations

Data analysis will be performed according to the Sponsor's or its representatives' Standard Operating Procedures (SOPs).

Details of statistical parameters and methods to be applied will be provided in a detailed Statistical Analysis Plan (SAP) prior to database lock (unblinding). The general analytical approach for all endpoints will be descriptive in nature.

Unless otherwise stated, the following statistical approaches will be taken:

- Continuous variables: Descriptive statistics will include the number of non-missing values, mean, standard deviation (SD), median, minimum, and maximum. The minimum and maximum values will be presented to the same number of decimal places as recorded in the CRF; mean, median, and SD will be presented to one more decimal place than the raw data.
- Categorical variables: Descriptive statistics will include frequency counts and percentages per category. Percentages will be rounded to one decimal place, with the denominator being the number of subjects in the relevant population.
- Imputation: No missing data will be imputed.
- PK data: Descriptive statistics will include the coefficient of variation. Arithmetic mean and SD will be substituted with geometric mean and SD for all PK-concentration descriptive statistics.
- Confidence intervals (CIs): CIs will be two-sided and will use 95% confidence levels. Any analyses requiring significance testing will use a two-sided test at the 5% significance level.
- Baseline: Baseline will be defined for each patient and will be defined as the last available, valid, non-missing assessment prior to start of first study-drug administration. Unknown, Not Done, Not Applicable, and other classifications of missing data will not be considered when calculating Baseline observations. However, valid categorical observations will be considered for Baseline calculations.
- Analyses: Parametric tests will be used where all statistical requirements are met (e.g., normal distribution). In the event that statistical requirements are not met, non-parametric alternatives will be utilized.

12.1 Sample Size

For the double-blind cohort, a sample size of 75 subjects was selected (25 subjects per treatment arm).

Allowing for a dropout rate of 10% the following sample-size sensitivity calculations were based on a minimum number of 22 subjects per treatment group completing the trial.

A 5% difference in total liver fat content is the minimal appreciable difference that would be considered clinically relevant between the active treatment arms and the placebo treatment group. If the NGM282 3-mg and 6-mg groups are assumed to have at least a 6% reduction in liver fat when compared to Baseline along with a reduction of 1% or less from Baseline in the placebo group, with a 5% level of significance, the following illustrates sample-size

power calculations based on varying common standard deviations to achieve an overall (overall F-test) statistically significant treatment effect:

	Mean Absolute Change from Baseline					
Method	NGM282 6 mg	NGM282 3 mg	Placebo	Common SD	Effect Size	Power
One-way	6%	6%	1%	8%	0.0868	54%
analysis of	6%	6%	1%	7%	0.1134	66%
variance	6%	6%	1%	6%	0.1543	80%
(equal n's)	6%	6%	1%	5%	0.2222	92%

SD = standard deviation.

A maximum sample size of 100 subjects was selected (with a minimum of 15 subjects per treatment arm, up to a maximum of 25 subjects per treatment arm) for the single-blind cohort design.

The sample size for the open-label single-blind cohort was not based on a formal sample-size calculation. Instead, it was based on the results of the interim analysis that was conducted when ~15 subjects per arm had completed 12 weeks of treatment. Although the results of this interim analysis are still blinded, the magnitude of the treatment differences observed indicate that a sample size of 15–20 subjects per treatment arm is sufficient to give an initial indication of efficacy for further exploration.

The sample size of the placebo-controlled 24-week histology cohort is based on 1) 12-week histologic response data from the 3-mg cohort and 2) estimated placebo histologic response rates from controlled Phase 2 studies in NASH. Preliminary 12-week histologic response data (n=16) demonstrated that 50% of subjects had a 1-stage improvement in fibrosis with no worsening of NASH or resolution of NASH with no worsening of fibrosis. The placebo histologic response rates from recent Phase 2b trials of obeticholic acid, cenicriviroc, liraglutide, and selonsertib were 14%–20% at timepoints ranging from 24 to 72 weeks. Based on these data, the assumptions of calculated sample-size estimates for 24-week efficacy used an NGM282 response of 50% versus 15% for placebo utilizing 80% power and alpha=0.05 with a 2:1 randomization scheme. Assuming a 15% drop-out rate, the planned sample size of 50 NGM282-treated subjects and 25 placebo subjects is sufficient to evaluate efficacy and support powering estimates for a late-stage clinical trial.

12.2 Randomization and Enrollment

For the double-blind cohort, at Day 1 all eligible subjects will be randomized via IWRS to one of the three treatment arms (NGM282 3 mg, NGM282 6 mg, or placebo) in a 1:1:1 ratio. The proportion of subjects with diabetes (categorized on a dichotomous scale) will be balanced across the three groups to ensure an even distribution across the three groups.

Diabetes status for balancing ("no diabetes" or "diabetes"), will be based on medical history, Screening labs, current medications, and clinical assessments.

The single-blind cohort is not randomized. Subjects will initially be enrolled sequentially into dosing Group 1 and enrollment will be continuous within and between each dosing groups. Sequencing of the dosing Groups 2 and 3 will be based on PD and safety parameters from dosing Group 1 and may run in parallel to each other. A fourth optional dosing group may be conducted based on the safety/tolerability, imaging data and histology (dosing Group 3 only) data from the prior 3 dosing groups. Dosing Group 4 will be initiated only after all subjects in Cohort 3 have been enrolled and a minimum of 10 subjects have completed 12 weeks of treatment in order to do a preliminary review of key data. Dosing group sequence and individual subject treatment assignment will be blinded only study subjects throughout the study period.

For the placebo-controlled 24-week histology cohort, at Day 1 all eligible subjects will be randomized via IWRS to one of the two treatment arms (NGM282 1 mg or placebo) in a 2:1 ratio. The Sponsor, study sites, and subjects will be blinded to treatment assignment. The randomization schedule will be stratified by subject's fibrosis stage 2 or 3 based on the screening qualification liver biopsy.

12.3 Test of Hypothesis and Significance Levels

The null hypothesis being tested for this study will be that there is no difference in the absolute change in liver fat content from Baseline between the NGM282 and the Placebo treatment groups at EOT for the double-blind cohort. The alternative hypothesis being tested will be that there is at least a 5% difference in the absolute change in liver fat content from Baseline between the NGM282 and the Placebo treatment arms at Week 12 for the double-blind cohort. A two-sided analysis will be conducted at a 5% significance level.

Comparisons across the cohorts will be exploratory and further outlined in the SAP.

12.4 Study Populations

The study populations are detailed below. Details of any other populations for analysis will be described in the SAP.

12.4.1 Intent-to-Treat Population

All randomized subjects in the double-blind and placebo-controlled 24-week histology cohorts) will be included in the Intent-to-Treat (ITT) population. All Baseline characteristics and demographic data will be summarized using the ITT population. The ITT population will be based on randomized treatment if this differs from actual treatment received.

12.4.2 All Patients Population

For the open-label single-blind cohort, all enrolled subjects will be included in the All Patients population. All Baseline characteristics and demographic data for the open-label single-blind cohort will be summarized using the All Patients population. The All Patients population will be based on enrolled treatment if this differs from actual treatment received.

12.4.3 Safety Population

All randomized/enrolled subjects who receive at least one dose (full or partial) of study drug and have at least one post-dose safety evaluation will be included in the Safety population. All safety endpoints will be summarized using the Safety population and will be based on actual treatment received if this differs from the randomized/enrolled treatment.

12.4.4 Efficacy Population

All randomized/enrolled subjects who receive at least one dose (full or partial) of study drug and have at least one valid, non-missing post-dose efficacy/PD parameter value will be included in the Efficacy population. All efficacy and PD endpoints will be summarized and analyzed using the Efficacy population. This will be the main population for the analysis of efficacy and PD endpoints. The Efficacy population will be based on randomized/enrolled treatment if this differs from actual treatment received.

12.4.5 Per Protocol Population

The Per Protocol (PP) population will constitute a subset of the Efficacy population and will include subjects that have at least one valid, non-missing post-dose liver fat content measurement. Subjects in the Efficacy population who deviate from the conduct of the study or have an AE deemed by the Medical Monitor to be impactful on the primary endpoint will be excluded from the PP population. This will be the secondary population for the analysis of efficacy and PD endpoints. The PP population will be based on actual treatment received if it differs from that to which the patient was randomized/enrolled.

12.4.6 Liver Histology Population

The liver histology population will constitute a subset of patients in the Efficacy population and will include patients who have at least one valid, non-missing Baseline and EOT liver biopsy. Subjects in the Efficacy population who deviate from the conduct of the study or have an AE deemed by the Medical Monitor to be impactful on the primary endpoint will be excluded from the PP population. This will be the secondary population for the analysis of efficacy and PD endpoints. The PP population will be based on actual treatment received if it differs from that to which the patient was randomized/enrolled.

12.4.7 Pharmacokinetic Population

All randomized/enrolled subjects who receive at least one dose (full or partial) of drug, with a pre-dose (Baseline) blood draw, and at least one qualified (above the limit of quantification) post-dose sample will be included in the PK population. Subjects with protocol violations will be assessed by the medical monitor for inclusion in the PK population. PK summaries and analyses will be conducted using the PK population. The PK population will be based on actual treatment received if it differs from that to which the patient was randomized/enrolled.

12.5 Treatment Exposure

Individual data listings for treatment exposure will be presented for each subject. Treatment exposure will be summarized as extent of exposure to the study drug. Measures of extent of exposure include the total number of doses per subject and compliance. Treatment compliance is defined as the number doses administered per protocol/number of doses prescribed per protocol. Treatment exposure will be summarized using the Safety population by actual treatment.

12.6 Patient Disposition

Individual data listings for patient disposition will be presented for each patient, including enrollment date, treatment start date, treatment discontinuation date, discontinuation reason, and population flags. The number and percentage of patients entering and discontinuing the study will be presented by randomized treatment group for the double-blind and placebo-controlled 24-week histology cohorts and by enrolled treatment group for the open-label single-blind cohort. The reasons for discontinuation will also be summarized. Patient disposition will be summarized using the ITT population for the double-blind and placebo-controlled 24-week histology cohorts and the All Patients population for the open-label single-blind cohort.

12.7 Protocol Deviations

Individual data listings for protocol deviations will be presented for each patient. Protocol deviations will be summarized using the ITT population for the double-blind and placebo-controlled 24-week histology cohorts and the All Patients population for the open-label single-blind cohort.

12.8 Demographic Analysis

Individual data listings for demographic and Baseline characteristics will be presented for each patient. Demographic and Baseline characteristics will be descriptively summarized by randomized treatment group for the double-blind and placebo-controlled 24-week histology

cohorts and by enrolled treatment group for the open-label single-blind cohort. Quantitative and/or categorical summaries will be presented for demographics, medical history, and other Baseline characteristics. Demographic and Baseline characteristics will be summarized using the ITT population for the double-blind and placebo-controlled 24-week histology cohorts and the All Patients population for the open-label single-blind cohort.

12.9 Efficacy and Pharmacodynamics

Individual data listings for efficacy and PD variables will be presented for each patient. Efficacy and PD summaries and analyses will use the Efficacy population.

12.9.1 Efficacy and Pharmacodynamic Endpoints

The primary efficacy endpoint for this study will be the absolute change in liver fat content as measured by MRI-PDFF in patients subjects with histologically confirmed NASH after 12 or 24 weeks of treatment.

Secondary Objectives:

- Evaluate the percentage change in absolute liver fat content at EOT.
    - In the open-label single-blind cohort, additional evaluations will be performed at Weeks 6 and 18.
    - In the placebo-controlled 24-week histology cohort, additional evaluations will be performed at Weeks 6, 24, and 30.
- Evaluate the percentage of normalization for liver fat content at EOT.
- Evaluate the change in liver fat content response rate as defined by a ≥ 5% decrease in absolute liver fat content.
- Evaluate the absolute and percentage changes from Baseline to EOT as well as the percentage of normalization of the following parameters: ALT, AST, triglycerides, bilirubin (total and direct), and GGT. Percentage of normalization will also be investigated for a clinically meaningful threshold for triglycerides.
- Evaluate the absolute and percentage changes from Baseline to EOT of the following:
    - Total cholesterol, HDL-C, LDL-C, triglycerides, and lipoprotein particles
    - FFAs
    - Fasting blood glucose, insulin levels, [redacted], and HOMA-IR
    - Pro-C3 and ELF scores (Placebo Controlled 24 Week Histology Cohorts)
    - Body weight, BMI, and waist circumference
    - C4 and serum bile acids
    - Bile-mediated absorption as measured by vitamin D, INR, and fecal fat content
- Evaluate the liver histologic response in Placebo Controlled 24 Week Histology Cohorts
    - Improvement in liver fibrosis by ≥ 1 stage by NASH Clinical Research Network (CRN) criteria with no worsening of steatohepatitis

  - Resolution of NASH (defined as an NAS score of 0 or 1 for inflammation and 0 for ballooning) with no worsening of fibrosis as determined by the NASH CRN criteria.

- Evaluate the exposure of NGM282 in patients with NASH.
  - In the double-blind and placebo-controlled 24-week histology cohorts, NGM282 exposure will be compared to placebo at 2 hours post-dose at Day 1 and EOT and pre-dose at all on-treatment study visits.
  - In the open-label single-blind cohort, NGM282 exposure will be compared across the dosing groups at 2 hours post-dose at Day 1 and Week 12 and pre-dose at all on-treatment study visits. Additional PK samples will be collected at Baseline and 1, 2, 4, 8, and 12 hours post-dose on Day 1 and Week 6 in a subset of subjects in each dosing group.

Exposure of all doses from both double-blind and open-label single-blind cohorts will be compared to each other as well as to exposure in other study populations treated with NGM282 (Studies 12-0101, 13-0102, 13-0103, 14-0104, and 15-0106).

The impact of rosuvastatin administered in response to increases in total cholesterol and LDL-C from NGM282 treatment will be evaluated.

Exploratory Parameters:

- [redacted]

12.9.2 Analysis of Primary Endpoint

The analysis of the primary endpoint will be based on the Efficacy population.

The absolute change in liver fat content from Baseline to EOT will be compared between treatment groups using an analysis of covariance (ANCOVA) model with treatment group and diabetic status (double-blind cohort only) as cofactors and Baseline endpoint as a covariate. Least square means with standard errors (SEs), differences in least square means with SE, 95% CIs for the difference in least square means, and corresponding p-values will be presented. Further covariates/cofactors may be included in the modeling depending on the relevance to the endpoint analyzed and will be further described in the SAP.

In cases where the parameters do not follow a normal distribution, a non-parametric approach will be followed to analyze the difference between treatment groups.

The primary analysis for the primary endpoint will be repeated for the Per Protocol population.

12.9.3 Analysis of Secondary Endpoints

The analysis of secondary PD endpoints will be based on the Efficacy population, for all three cohorts separately.

For continuous secondary endpoints the same method of analysis as for the primary endpoint will be followed. Further covariates/cofactors may be included in the modeling depending on the relevance to the endpoint analyzed and will be further described in the SAP.

Categorical secondary endpoints (percentage of normalization) will be analyzed through a chi-square test. The difference between proportions along with 95% CIs for the difference between proportions will be presented by treatment-group comparisons.

The analyses in the open-label single-blind cohorts will be stratified by statin use at Baseline whereas they will be stratified by fibrosis stage in the placebo-controlled 24-week histology cohort. The effect of statin use on lowering LDL cholesterol will also be explored both the open-label single-blind and placebo-controlled 24-week histology cohorts. In addition, sensitivity analyses will be performed to investigate the effect on the efficacy endpoints of statin use in the open-label single-blind cohorts and fibrosis stage on the placebo-controlled 24-week histology cohort.

Comparisons between the 3 cohorts will be performed and further detailed in the SAP.

12.9.4 Analysis of Exploratory Endpoints

The analysis of exploratory endpoints will be based on the Efficacy population.

For continuous exploratory endpoints the same method of analysis as for the primary endpoint will be followed. Further covariates/cofactors may be included in the modeling depending on the relevance to the endpoint analyzed and will be further described in the SAP.

12.10 Safety

Safety and tolerability will be assessed by clinical review of the following parameters: AEs, clinical laboratory tests, physical examination, and vital signs. All safety analyses will be conducted using the safety population.

12.10.1 Adverse Events

AEs, including serious AEs, will be coded using the MedDRA. The number and percentage of subjects experiencing an AE will be summarized for each system organ class (SOC) and preferred term (PT) by treatment group. In addition, AEs will be tabulated according to intensity, causality, and relation to the study drug. Individual data listings for AEs will be presented for each subject.

All AE summaries will be restricted to TEAEs only. TEAEs are defined as AEs that commence on or after the time of start of first study-drug administration. AEs without an onset date or time will be defined as treatment emergent, except if an incomplete date (e.g., month and year) clearly indicates that the event started prior to the start of first administration of study drug or if the AE stop date indicates that the event started or stopped prior to the start of first administration of study drug.

For the summaries of AEs, subjects who experience the same AE (in terms of the MedDRA preferred term) more than once will be counted only once for that event. Separate summaries will be provided for AEs by intensity, causality, and relationship to study drug.

All AEs will be listed. SAEs will be summarized and listed.

12.10.2 Clinical Laboratory Evaluations

The absolute and percentage changes from Baseline to EOT and EOS of total cholesterol, HDL-C, LDL-C, and lipoprotein particles will be analyzed through inferential statistics and will be based on the Safety population.

Observed values and absolute changes from Baseline to EOT and EOS for routine chemical laboratory values will be summarized descriptively at each time point for each treatment group and overall. Shift tables may also be presented for select chemistry and hematology laboratory parameters, as defined in the SAP.

Individual data listings of laboratory results will be presented for each subject. Laboratory values will be compared to normal ranges; out-of-range and clinically significant laboratory values will be identified in the listings.

12.10.3 Physical Examinations

Individual data listings for physical examination results will be presented for each subject.

12.10.4 Vital Signs

Observed values as well as absolute changes from Baseline will be summarized descriptively for all vital-sign parameters, by time point and treatment group. Individual data listings will be presented for each subject.

12.10.5 Pregnancy Test

Individual listings for urine and serum pregnancy test data will be presented for each subject.

12.10.6 Electrocardiogram

Observed values as well as absolute changes from Baseline will be summarized descriptively for all ECG parameters, by time point and treatment group. Individual data listings will be presented for each subject.

12.10.7 Injection-Site Reactions

Frequency tabulations of ISR results will be presented at each time point by treatment group.

12.10.8 Concomitant Medications

Concomitant medications will be classified using the current version of the World Health Organization Drug Dictionary Enhanced (2012). Concomitant medications are medications taken at least once from 28 days prior to Screening through the End of Study visit. Medications stopped on the 28 days prior to Screening time point will not be considered a concomitant medication.

Individual data listings will be presented for each subject, with separate listings for prior medications and concomitant medications. In addition, concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) classes and PT using frequency counts and percentages. For the summaries of concomitant medications, subjects who take the same medication (in terms of the preferred term) more than once will be counted only once for that medication.

12.11 Pharmacokinetics

12.11.1 Trough Serum Concentrations (All Subjects)

The following PK parameters will be calculated using validated PK software, WinNonlin, Version 5.3 (or higher; Pharsight Corporation; Cary, NC, U.S.):

- Day 1; Weeks 1, 2, 4, 8, 12, 18, and 24: trough concentration (C_{trough})
- Day 1 and Week 12 or Week 24: C_{trough}; concentration at 2 hours post-dose ($C_{2h\ post\text{-}dose}$)

PK data will be used to evaluate the accumulation of NGM282 in the plasma of NASH patients following multiple-dose administration at 3 and 6 mg per day. This will be done by comparing the steady-state trough NGM282 levels in NASH patients to results obtained on Day 1 in the same subject and, more generally, in the dosing cohort. In addition, determination of NGM282 concentrations 2 hours post-dose on Day 1 and EOT will enhance information obtained on accumulation and provide an indication of expected maximum drug concentration (C_{max}) in patients. This information will be directly compared to Phase 1 results obtained in healthy volunteers as well as those obtained in patients with T2D, PBC, and primary sclerosing cholangitis. In addition, PK data will be used to explore PK/PD correlations in terms of drug efficacy and toxicity, where data allow. Actual sample times will be used in the data analysis.

12.11.2 Single-Dose Pharmacokinetics (Open-Label Single-Blind Subjects)

The Day 1 PK data will be used to evaluate the single-dose PK of NGM282 in PBC patients at 0.3, 1, and 3 mg per day, using the PK population. For each subject, the following PK parameters will be calculated, whenever possible, based on the serum concentrations of NGM282 collected at pre-dose and 1, 2, 4, 8, and 12 hours after dosing on Day 1.

- C_{max} - maximum observed concentration
- T_{max} - time to maximum concentration
- $AUC_{0–t}$ - area under the concentration–time curve from Hour 0 to the last measurable concentration, calculated using the linear trapezoidal rule
- $AUC_{0–\infty}$ - area under the concentration–time curve extrapolated to infinity, calculated using the formula:

  $$AUC_{0–\infty} = AUC_{0–t} + \frac{C_t}{\lambda_z}$$

  where C_t is the last measurable concentration and λ_Z is the apparent terminal elimination rate constant
- $t_{1/2}$ - apparent terminal elimination half-life, where $t_{1/2} = (\ln 2)/\lambda_Z$
- CL/F - clearance divided by the bioavailable fraction calculated using this formula: $Dose/AUC_{0–\infty}$
- V_z/F - volume of distribution based on the terminal portion of the concentration–time curve divided by the bioavailable fraction, $Dose / (AUC_{0–\infty} \times \lambda_z)$

The effect of dose level on NGM282 exposure will be assessed by evaluating C_{max} and $AUC_{0–t}$. Any substantial change in $t_{1/2}$, CL/F, or V_z/F with dose will also be noted.

Further details will be specified in the SAP.

12.11.3 Multiple-Dose Pharmacokinetics (Open-label Single-blind Subjects)

Week 6 PK data will be used to evaluate the effect of repeat dosing and potential accumulation of NGM282 following administration at 0.3, 1, and 3 mg per day, using the PK population. For each subject, the same PK parameters as listed in Section 12.11.2 will be calculated whenever possible, based on the serum concentrations of NGM282 collected at pre-dose and 1, 2, 4, 8, and 12 hours after dosing on Week 6. Where possible, $AUC_{0-\infty}$, $t_{1/2}$, CL/F, and V_z/F will be used for the evaluation of time invariance in PK characteristics. Accumulation will be assessed by calculating $C_{max,\ Week\ 4}/C_{max,\ Day\ 1}$ and $AUC_{0-t,\ Week\ 4}/AUC_{0-t,\ Day\ 1}$ for each subject.

In addition to the Week 6 versus Day 1 comparison, accumulation will also be assessed by comparing the trough and 2-hour post-dose NGM282 levels collected over the course of the study.

PK parameters will be estimated, where appropriate, using validated commercial software. Additional software, if required, will be detailed in the SAP. Other parameters may be added as appropriate. PK analysis will use actual times as recorded on the CRF.

12.12 Interim Analysis

A single interim analysis (IA) is planned to be conducted in the double-blind cohort after approximately 12 subjects per arm have completed 12 weeks of treatment. The final analysis of the double-blind cohort is planned to be conducted after all double-blind subjects have completed Week 16. The IA will include review of all safety and selected efficacy endpoints. The final analysis of the double-blind cohort will review all endpoints (safety, efficacy, and exploratory).

The double blind will be maintained for the IA as the results in the summary listings and tables will be presented only by treatment group. The data will be fully unblinded at the final analysis of the double-blind cohort as the database will include all randomized and completed have undergone a soft-lock at that time.

There will be no formal IAs performed in the open-label single-blind cohort.

A single IA is planned to be conducted in the placebo-controlled 24-week cohort after at least 50% subjects (2:1 randomization) have completed 24 weeks of treatment. The IA will include review of safety and selected efficacy endpoints by treatment group. The IA is being conducted only for internal planning purposes and the study will not be stopped early based on the results of the IA. Therefore, no formal hypothesis testing will occur with no effect on available alpha for the final planned analyses. The final analysis is planned to be conducted

after all subjects have completed Week 30. Results for individual subjects will not be shared with study investigators.

Further details of the IA and final analyses, including statistical considerations and analyses, will be included in the SAP.

13 Administrative Aspects

13.1 Protocol Adherence

The PI must adhere to the protocol as detailed in this document and agree that the Sponsor must approve any changes to the protocol prior to seeking approval from the EC. No alterations in the protocol will occur without agreement between the Sponsor and the PI. No alterations in the protocol affecting patient safety will occur without the express written approvals of the Sponsor, PI, and EC.

13.2 Disclosure

All information provided regarding the study as well as all information collected/documented during the course of the study will be regarded as confidential. The PI agrees not to disclose such information in any way without prior written permission from the Sponsor.

Any publication of the results either in part or in total (articles in journals or newspapers, oral presentations, abstracts, etc.) by the PI or their representative(s) shall require prior notification and review within a reasonable time frame by the Sponsor and cannot be made in violation of the Sponsor's confidentiality restrictions or to the detriment of the Sponsor's intellectual property rights.

13.3 Monitoring

The Sponsor's or designee's Clinical Research Associate (CRA) will be responsible for monitoring this clinical trial. The CRA will monitor the study conduct, proper CRF and source documentation completion and retention, and accurate study-drug accountability. To this end, the CRA will visit the study site at suitable intervals and be in frequent contact through verbal and written communication. The PI will grant access to all documents (related to the study and the individual subjects) at any time these are requested. In turn, the CRA will adhere to all requirements for patient confidentiality as outlined in the ICF. The PI and PI's staff will be expected to cooperate with the CRA, to be available during a portion of the monitoring visit to answer questions, and to provide any missing information.

13.4 Ethics Committee

This protocol, the informed consent document, and all relevant supporting data must be submitted to the EC for approval. EC approval of the protocol, informed consent document, and any advertisement used to recruit study patients must be obtained before the study may be initiated.

The PI is responsible for keeping the EC advised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, at least once a year. The PI is also responsible for notifying the EC of any reportable AEs that occur during the study.

13.5 Informed Consent

This study will be conducted in compliance with International Conference on Harmonisation (ICH) E6 Good Clinical Practice: Consolidated Guidelines pertaining to informed consent. At the first visit, prior to initiation of any study-related procedures, patients must give their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits.
The informed consent document must be signed and dated by the patient and PI, or designee, prior to study participation. A copy of the informed consent document must be provided to the patient. Signed consent forms must remain in the patient's study file and be available for verification by Sponsor or its representative at any time.

13.6 Records

The results from Screening and data collected during the study will be recorded in the patient's CRF. To maintain confidentiality, the patients will be identified only by numbers and initials.

The completed CRFs will be transferred to the Sponsor or designee. Copies of each CRF will be retained by the PI. All source documents, records, and reports will be retained by the clinic.

All primary source data or copies thereof (e.g., laboratory records, CRFs, data sheets, correspondence, photographs, and computer records) that are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report will be retained in the clinic archives.

Sponsor will inform the PI of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest (longest) standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or Sponsor standards/procedures; otherwise, the

retention period will default to the retention period of 15 years following completion of the clinical trial.

13.7 Financing and Insurance

The financing and insurance for this study are outlined in the Clinical Trial Research Agreement.

Investigator Protocol Review and Signature Form

Protocol Number: 15-0105

Protocol Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Multiple-Center Study with Additional Open-Label Single-Blind and Placebo-Controlled 24-Week Histology Cohorts to Evaluate the Safety, Tolerability, and Efficacy of NGM282 Administered for Up to 24 Weeks in Patients with Histologically Confirmed Nonalcoholic Steatohepatitis (NASH)

I have read the above-mentioned Protocol Amendment 9 dated 29 March 2019

I agree to conduct the study as detailed herein and in compliance with ICH Guidelines for Good Clinical Practice and applicable regulatory requirements, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Principal Investigator (Please PRINT)

_____ _____

Principal Investigator (Signature) **Date**

_____

Name of Institution (Please PRINT)

Sponsor Protocol Approval and Signature Page

Protocol Number: 15-0105

Protocol Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Multiple-Center Study with Additional Open-Label Single-Blind and Placebo-Controlled 24-Week Histology Cohorts to Evaluate the Safety, Tolerability, and Efficacy of NGM282 Administered for Up to 24 Weeks in Patients with Histologically Confirmed Nonalcoholic Steatohepatitis (NASH)

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[redacted]

08-April-2019
Date

Senior Director, Clinical Development
NGM Biopharmaceuticals, Inc.

14 References

14.1 Clinical Study References

Study No.	Phase	Study Title	Study Population
12-0101	1	A Phase 1 Randomized, Double Blind, Placebo Controlled, Single Ascending Dose and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of NGM282 in Healthy Adult Participants	Normal volunteers
13-0102	2a	A Randomized, Double Blind, Placebo Controlled, Parallel Group, Multiple Center Study to Evaluate the Safety, Tolerability, and Activity of NGM282 Administered for 28 Days to Participants with Type 2 Diabetes Mellitus	T2D
13-0103	2a	A Phase 2, Randomized, Double Blind, Placebo Controlled, Parallel Group, Multiple Center Study to Evaluate the Safety, Tolerability, and Pharmacodynamic Activity of NGM282 in Combination with Ursodeoxycholic Acid (UDCA) Administered for 28 Days in Patients with Primary Biliary Cirrhosis (PBC)	PBC
14-0104	2b	A Phase 2, Multicenter Study to Evaluate Four Doses of NGM282 Administered For 52 Weeks in Patients with Primary Biliary Cirrhosis (PBC)	PBC
15-0106	2	A Phase 2, Randomized, Double Blind, Placebo Controlled, Parallel Group, Multiple Center Study to Evaluate the Safety, Tolerability, and Efficacy of NGM282 Administered for 12 Weeks in Patients with Primary Sclerosing Cholangitis (PSC)	PSC

14.2 Nonclinical Study References

Study No	Study Title
Study 11-MP-NGM282-1001	Direct Effects of NGM282 on Mouse and Human Adipocytes
Study 11-MP-NGM282-1002	Analysis of NGM282 Binding to Fibroblast Growth Factor Receptors
Study 11-PD-NGM282-1001	A 24-week Study of Ectopic NGM282 Expression following Intravenous Adeno-Associated Viral Delivery to db/db Mice
Study 11-PD-NGM282-1003	A Single or 14-Day Efficacy Study of NGM282 Following Subcutaneous Administration in ob/ob Mice
Study 11-PD-NGM282-1004	Effects of NGM282 on Glucose Metabolism and Body Weight Following 14-Day Daily Subcutaneous Administration in Diet-Induced Obese (DIO) Mice
Study 11-TX-NGM282-1002	A 28-Day Subcutaneous Toxicity and Toxicokinetic Study with NGM282 in Cynomolgus Monkeys with a 14-Day Recovery Phase
Study 12-MP-NGM282-1006	Effects of NGM282 Treatment on CYP7a1 Expression in Primary Mouse, Rat, and Human Hepatocytes
Study 13-MP-NGM282-1004	NGM282 Activation of Elk-1 in L6 Cells Expressing Mouse, Rat, Rabbit, Cynomolgus, or Human FGFR1c-βklotho Co-Receptors
Study 13-MP-NGM282-1005	Activation of FGFR4-β-klotho-Mediated Signaling by NGM282 in a Rat Myoblast Cell Line
Study 13-PD-NGM282-1007	A 24-Week Study of Ectopic NGM282 Expression following Intravenous Adeno-Associated Viral Delivery in FXR-deficient Mice
Study 13-TX-NGM282-1004	A 13/26-Week Subcutaneous Toxicity and Toxicokinetic Study of NGM282 in Cynomolgus Monkey

14.3 Literature References

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15 Appendices

Appendix A. NASH Clinical Research Network (CRN) NAFLD Activity Score and Fibrosis Score

Steatosis	S Score	Lobular Inflammation	L Score	Hepatocyte Ballooning	B Score
< 5%	0	None	0	None	0
5%–33%	1	< 2	1	Few ballooned cells	1
34%–66%	2	2–4	2	Many ballooned cells	2
≥ 66%	3	> 4	3	—	—

NAFLD = nonalcoholic fatty liver disease.

Note: NAFLD activity grade score = total score: S + L + B (range 0–8).

Fibrosis Stage	Score
0	No Fibrosis
1a	Zone 3, Mild
1b	Zone 3, Moderate
1c	Periportal Only
2	Zone 3 and Periportal
3	Bridging
4	Cirrhosis

Appendix B. Food and Drug Administration Toxicity Grading Scale: Clinical Abnormalities in Local Injection-Site Symptom Assessments

Local Reaction to Injection Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever more than 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness [a]	2.5–5 cm	5.1–10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling [b]	2.5–5 cm and does not interfere with activity	5.1–10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

ER = emergency room.
Note: The FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers enrolled in Preventive Vaccine Clinical Trials can be found at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074775.htm.
[a.] In addition to grading the measured local reaction at the greatest single diameter, the measurements should be recorded as a continuous variable.
[b] Induration or Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Appendix C. Rosuvastatin Package Insert

The package insert for rosuvastatin currently being used in the open-label single-blind cohort can be found at the following web link:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/079167Orig1s000lbl.pdf

The package insert for rosuvastatin currently being used in the placebo-controlled 24-week histology cohort can be found at the following web link:

http://www.torrentian.com/pisheet/Upload/PI_Sheet_US/181_2.pdf

Appendix D. Ezetimibe Package Insert

The package insert for ezetimibe related to the placebo-controlled 24-week histology cohort can be found at the following web link:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021445s019lbl.pdf

Appendix E. Prohibited Hepatotoxic Agents

All other hepatotoxic agents will be left to the discretion of the PI. There should be clear documentation in the patient study records of Investigator approval of use.

Generic Name	Drug Class/Common Use
Acetaminophen > 3000 mg/day	NSAID
Albendazole	Anthelmintics (parasitic infections)
Allopurinol	Antigout
Amiodarone	Antiarrhythmic
Amodiaquine,	Antimalarial
Azathioprine/6-Mercaptopurine	Antineoplastic/Antirheumatic, autoimmune
Buspirone	Sedatives, hypnotics, Psychoactive drug – for anxiety
Busulfan	Antineoplastic/Alkylating, cancer
Carbamazepine	Anticonvulsant
Chemotherapies	
Chlorpromazine	GI, antipsychotic
Dantrolene	Muscle relaxant
Didanosine	Antiviral
Dimethyl Fumarate	For MS
Disufiram	Alcohol Deterrents
Dronedarone	Antiarrhythmic (AFib/flutter)
Efavirenz	Antiviral
Fenofibrate	Anti-lipemic Hypertriglyceridemia, hypercholesterolemia
Floxuridine	Antineoplastic, cancer
Flutamide	Antineoplastic, nonsteroidal antiandrogen (NSAA)
Glatiramer acetate	For MS
Gold Salts	Antirheumatic, RA
Halothane	Anesthetics for surgery
Hydralazine	Antihypertensive
Infliximab	Antirheumatic, Dermatologic, GI
Interferon alpha	Antiviral
Interferon beta	MS
Isoniazid	Anti TB
Methotrexate	Antineoplastic, Antirheumatic, Dermatologic
Methyldopa	Antihypertensive
Nefazodone,	antidepressant
Nevirapine	Anti-viral (HIV/AIDS therapy)
Nimesulide,	NSAID – COX-2
Norethisterone	For menstrual issues
Phenytoin	anticonvulsant
Pirfenidone	Pulmonary fibrosis
Propylthiouracil	Antithyroid
Pyrazinamide	Anti TB
Quinidine	Antiarrhythmic
Rifampin	Anti TB
Sulfasalazine	Anti-infective (DMARD, anti-inflammatory)
Suramin	Injectable – antiprotozoal agent
Thioguanine	Antineoplastic/Antirheumatic,
Ticlopidine	Antithrombotic, platelet inhibitor
Valproate	Anticonvulsant (epilepsy), mood stabilizer (Bipolar)